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Full Name of Author — Nom complet de l'auteur
JOSEP ARMENGOL

Date of Birth — Date de naissance
28-10-1951

Country of Birth — Lieu de naissance
SPAIN

Permanent Address — Résidence fixe
MONTSERRAT An-4-1-A
MONTCADA - BARCELONA - SPAIN

Title of Thesis — Titre de la thèse
Studies of hemodynamics gas exchange and lung mechanics with metal bellows oscillatory ventilation in dogs

University — Université
Alberta

Degree for which thesis was presented — Grade pour lequel cette thèse fut présentée
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1985

Name of Supervisor — Nom du directeur de thèse
E.G. KING

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STUDIES OF HEMODYNAMICS, GAS EXCHANGE AND LUNG MECHANICS WITH METAL BELLOWS OSCILLATORY VENTILATION IN DOGS

by

© Josep Armengol

A THESIS

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PERMANENT ADDRESS:

6-106 Clinical Sciences Bldg.
Pulmonary and Intensive Care
Division, University of Alberta
Edmonton, Alberta, Canada.

DATED 1984

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16 Nov 1984

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FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled "Studies of Hemodynamic, Gas Exchange and Lung Mechanics with Metal Bellows Oscillatory Ventilation in the Dog", submitted by Josep Armengol, for the requirements for the degree of Doctor of Philosophy in Medical Sciences.

E.G. King
SUPERVISOR

R.L. Jones
SUPERVISOR

A.B. Froese
EXTERNAL EXAMINER

A.C. Bryan

Michael Grace
D.M. Grace

D.L.J. Tyrrell
D.L. Tyrrell

DATE October 15, 1984

Dedico aquest treball als pares, ells m'han fet el que soc: un esser humà.

ABSTRACT

This thesis describes the use of a metal-bellows pump for high-frequency oscillatory ventilation (HFOV) of dogs. The pump was characterized *in vitro* and found to deliver a volume of 22 ml at 20 Hz and to have a tendency to increase lung-model pressure as frequency increased. The *in vivo* experiments proved that this ventilatory system is capable of maintaining adequate gas exchange over a range of frequencies between 15 and 30 Hz using a bias flow of 1 or 4 L/min. The HFOV system described has a tendency to increase mean lung volume ($\bar{V}_L$) and alveolar pressure ($\overline{\text{Palv}}$), which results in impairment of cardiovascular function, mainly decreased cardiac output and increased pulmonary vascular resistances. The decrease in cardiac output seems to be due to a decrease in left ventricular compliance, and the increase in pulmonary vascular resistances to the change in $\bar{V}_L$ and $\overline{\text{Palv}}$. The acute increase in pulmonary artery pressure induced by HFOV was not due to prostaglandin release. The changes in cardiovascular function induced by HFOV were directly correlated to both the increase in $\overline{\text{Palv}}$ and $\bar{V}_L$. The increase in $\overline{\text{Palv}}$ was found to be a more important factor in inducing the cardiovascular changes than the increase in $\bar{V}_L$ was The increase in $\bar{V}_L$ induced by HFOV was established in less than 1 min and remained stable for at least 16 min. The present HFOV system requires a mean airway pressure of at least 6 cm H_2O to maintain normal gas exchange which is higher than in other systems which have been described. It seems likely than HFOV performed at lower pressures induces little or no cardiovascular impairment. Comparison of the pressure and volume data of the respiratory system obtained during HFOV, with static compliance measurements suggest that the elastic characteristics of the respiratory system are not changed by HFOV

In this thesis, a model of saline lavage of dog lungs is described, in which HFOV induces higher arterial oxygenation and $\bar{V}_L$ than conventional ventilation, at similar mean airway pressures. The measurements of the mechanics of collateral channels suggest that HFOV increases the resistance to gas flow through them. The tracheal transport of two different sizes of particles was found to be influenced in a similar manner by HFO and conventional ventilation. This HFOV system induces a gradient in airway pressure causing mean distal pressures (and probably $\bar{P}$alv) to be higher than mean proximal pressure. A gradient in CO_2 concentration was also found in the airways during HFOV.

Other studies described in this thesis include: comparison of the bellows pump to a diaphragm ventilator; comparison of several methods to measure thoracic gas volume with a body plethysmograph; _in vitro_ study of the effects of thermistor vibration on thermodilution flow measurements; and description of an inexpensive flowmeter for measurement of low flows of gas.

PREFACE

This thesis consists of four parts: introduction, research description, overall discussion and appendices. The introduction is an exhaustive and critical review of high-frequency ventilation (HFV), with the following headings: Definition, Classification, History, Technical Aspects and Literature Review of high-frequency related research (including theoretical, animal and human studies). The references used for the introduction have been arranged in groups according to topics, and distributed as follows: Refs. 1 to 300, high-frequency jet ventilation (HFJV); Refs. 301 to 550, high-frequency oscillatory ventilation (HFOV); Refs. 551 to 600, review articles; Refs. 601 to 760, high-frequency positive-pressure ventilation (HFPPV); Refs. 761 to 800, external oscillatory ventilation (EOV); Refs. >800, articles not directly related to HFV.

The aim of the thesis' research was to develop a ventilator for high frequency oscillation studies, characterize its in-vitro performance and test it in-vivo for acute effects on several aspects of the cardiopulmonary function. The in-vitro tests were aimed mainly at understanding the factors that determined the volume delivered by the ventilatory circuit and the performance of the unidirectional valves (Appendix I). For the in-vivo tests, the dog was chosen as the experimental animal and the following null hypothesis was defined: "There is no difference between the cardiopulmonary effects of conventional ventilation (IPPV) and HFOV".

The first in-vivo study compared IPPV with several HFOV levels (Chapter 1). The results proved the null hypothesis to be false and suggested the important role of mean airway pressure ($\overline{\text{P}}\text{aw}$) and mean lung volume ($\overline{V}_L$) during HFOV (in subsequent experiments emphasis was put on the careful monitoring and documentation of these two parameters). In order to have an accurate assessment of $\overline{V}_L$, a body plethysmograph was constructed (Appendix II) and with it several methods of functional residual capacity (FRC) measurement were assessed (Appendix III). The plethysmograph was used to quantify time-related changes in $\overline{V}_L$ during HFOV (Chapter 2), to compare HFOV with IPPV plus positive end-expiratory pressure (PEEP) at the same $\overline{V}_L$ or $\overline{P}$aw (Chapter 3), and to study the changes in hemodynamic parameters induced by different levels of $\overline{P}$aw (and $\overline{V}_L$) during HFOV (Chapter 4).

To investigate the possibility that prostaglandins (PG) were involved in the increase in mean pulmonary artery pressure ($\overline{PAP}$) induced by HFOV, the effect of PG-production blockade was studied (Chapter 9C). The gradients in $\overline{P}$aw at different levels in the respiratory tree, created during HFOV, were quantitated in vivo and in isolated lung lobes (Chapter 9A), and several parameters of collateral ventilation were measured at various lung volumes during HFOV and PEEP (Chapter 6). To investigate the effect of HFOV on lung defense mechanisms, tracheal transport rates of two different radioactive markers were measured during spontaneous respiration, IPPV and HFOV (Chapter 7); also, an attempt was made to develop a method to study the effect of HFOV on lung clearance of radioactive particles (Chapter 9D). To further define its characteristics, the HFOV pump used for this thesis was compared to a standard commercially-available diaphragm oscillator (Chapter 8).

In preliminary trials, the effects of HFOV were studied on an oleic-acid lung injury model (Chapter 9F). In further experiments, a saline-lavage model of abnormal lung was studied in dogs (Appendix IV) and the effects of HFOV on this lung-injury model were quantitated (Chapter 5). Additional studies related to this thesis include: description of a circuit to ventilate small animals with a large-volume high-frequency oscillator (Chapter 9E); measurements of CO_2 gradients in the airways during HFOV (Chapter 9B); influence of vibration on the measurement of cardiac output by thermodilution (Appendix V); and description of a flowmeter for measurement of small flows (Appendix VI).

All the major research related to HFOV is described in independent chapters divided in standard sections: Introduction, Material and Methods, Results and Discussion. Even though each chapter includes a discussion of the research findings, it was considered convenient to add an overall discussion at the end of the thesis. Minor research related to HFOV has been condensed in one Chapter (Chapter 9), and research not directly relted to HFOV is described in the Appendices.

The findings described in this thesis might not necessarilly apply to all HFOV systems. As discussed in the Introduction, other authors have reported lower airway pressures and no impairment of the cardiovascular function.

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TABLE OF CONTENTS

Page

PREFACE vii

INTRODUCTION 1

DEFINITION AND CLASSIFICATION 2

Definition 2

Types of high-frequency ventilation
- High frequency jet ventilation 3
- High frequency positive-pressure ventilation 3
- High-frequency oscillatory ventilation 5
- Superimposed high-frequency ventilation 5
- External oscillatory ventilation 5
- Other types of high frequency ventilation 5
- Confusions about terminology 7

HISTORY

Basic concepts related to HFV 9

Early uses of HFV
- a) HFJV and HFPPV 11
- b) HFOV 11
- c) SHFV 12
- d) EOV 12

TECHNICAL ASPECTS

The ventilators
- a) HFJV and HFPPV 12
- b) HFOV 14
- c) SHFV 15
- d) EOV 15

The circuits
- a) Circuits for HFJV 15
- b) Circuits for HFPPV 16
- c) Circuits for HFOV 16
- d) Circuits for EOV 17

Other HFV types 17

Pressure waveform
- a) HFJV and HFPPV 17
- b) HFOV 18
- c) EOV 18

Entrainment 18

Conditioning inspired gases 19

Safety 20

Measuring ventilatory volumes during HFV 21
- a) HFJV 22
- b) HFPPV 22
- c) HFOV 23
- d) EOV 23

Accuracy of the volume measurements 23
- a) Rotameters 24
- b) Anemometers 24
- c) Pneumotachographs 24
- d) Water spirometers 25

Page

e) Plethysmographs and magnetometers 25
f) Testing the frequency response of the volume-measuring system 25
Measuring resting lung volume during HFV
a) Changes in resting lung volume 26
b) Functional residual capacity 26
Measuring airway and alveolar pressures during HFV
a) Measuring site 27
b) Frequency response 28
c) The catheter tip 28
d) Estimating Palv 29

MECHANISMS OF GAS EXCHANGE DURING HFV

Convection
a) Interregional gas exchange 30
b) Different inspiratory/expiratory flow profiles 31
c) Short bronchial path length 31
d) Studies supporting that convection is the main gas exchange mechanism during HFV 31
Diffusion
a) Oscillatory flow 32
b) Cardiogenic mixing 32
c) Taylor's dispersion 32
d) Studies supporting that diffusion is the main gas exchange mechanism during HFV 33
Diffusion plus convection 33

REVIEW OF RESEARCH ON HFV

Foreword 36
Theoretical studies
a) HFV-related physics 37
b) Electrical models 37
In vitro experiments
a) Lung model experiments 37
b) Isolated lung experiments 38
In vivo experiments: animal studies
I. -Species 39
II. -Pathologic lung models 39
III. -Findings in pathologic lung models
  a) Oleic acid pulmonary edema 42
  b) Saline-lavaged lungs 42
  c) Open-chested animals 42
  d) Broncohconstriction 42
  e) Other models 43
  f) Pathologic lung model data grouped according to ventilatory mode 43

IV. -Overall in vivo research
  a) Lung mechanics 43
(1) PRESSURE
  - Mean airway pressure 44
  - Peak airway pressure 45

$\overline{P}$aw Page

- Airway pressure gradients and alveolar pressure 45
- Esophageal and pleural pressures 46

(2) VOLUME

- Lung volume 47
- Compliance 48

(3) SURFACTANT 48

(4) COLLATERAL VENTILATION AND AIRWAY RESISTANCE 48

b) Gas exchange, transport and ventilation

- Arterial PaO_2 49
- Alveolar PO_2, oxygen gradients in the airway and alveolo-arterial O_2 difference 49
- O_2 delivery, O_2 consumption, mixed venous O_2 and arterio-venous O_2 difference 51
- $PaCO_2$ 51
- Alveolar PCO_2 and CO_2 gradients in the airway 52
- Dead space to tidal volume ratio, physiologic and anatomic dead space 53
- Shunt 54
- Ventilation/perfusion ratio 54

c) Hemodynamics

- Heart rate 54
- Systemic arterial pressure 56
- Pulmonary artery pressure and pulmonary vascular resistances 57
- Pulmonary artery wedged pressure 57
- Left ventricular end-diastolic pressure and left-atrial pressure 57
- Central venous pressure 57
- Cardiac output 57
- Left ventricular stroke work and right ventricular stroke work 59

d) Lung defense mechanisms

- mucociliary function 59
- Airway secretions 60

e) Miscellaneous

- Organ blood flow 60
- Lung water and lymph flow 60
- Intracraneal pressure 61
- Renal function 61
- Core temperature 61
- Long term effects 62
- Pathologic findings 62

Human Studies

I. Normal lung experiments

a) Technical and theoretical studies 63

b) Laryngoscopy 63

c) Bronchoscopy 64

d) Airway and chest surgery 64
e) Anesthesia 64
f) Cardiopulmonary resuscitation 64
g) Central respiratory insufficiency 64

II. Studies in humans with abnormal lungs

a) Acute respiratory insufficiency 64
b) Chronic obstructive pulmonary disease 65
c) Bronchopleural fistula 65
d) Infant respiratory distress syndrome 66
e) Airway secretions 66

ADVANTAGE INDICATIONS, DISADVANDTAGES
AND COMPLICATIONS OF HFV

Foreword 67

Advantages and indications

a) Surgery and anesthesia 67
b) Barotrauma 67
c) Miscellaneous 69

Disadvantages and complications

a) Technical 69
b) Barotrauma 70
c) Humidification 70
d) Trans-tracheal ventilation 70
e) Metabolic acidosis 70
f) Miscellaneous complications 71

COMPARISON OF DIFFERENT HFV MODES

HFJV, HFPPV and HFOV 71
Fast conventional ventilation 71
Superimposed HFV 72
External oscillatory ventilation 72

THE HFV LITERATURE

Methodology used for this review 73
Characteristics of the HFV literature 73

CONCLUSIONS77
REFERENCES78

Chapter 1: Gas exchange and cardiovascular function during HFOV 137
Chapter 2: Alveolar pressures and resting lung volumes during HFOV in dogs 154
Chapter 3: Comparing lung volumes and alveolar pressures during HFOV and PEEP 174
Chapter 4: Hemodynamic parameters measured during HFOV at different lung volumes and alveolar pressures 190
Chapter 5: Effects of HFOV and PEEP at constant $\bar{P}$aw on dogs with low-compliance lungs 204
Chapter 6: Collateral ventilation in dogs during HFOV 220
Chapter 7: Tracheal mucous transport of large and small particles during HFOV in dogs 238
Chapter 8: Comparison of the experimental bellows oscillator with a commercially-available diaphragm oscillator 257
Chapter 9: A) Airway pressure gradients created by HFOV 269

Page

B) Carbon dioxide gradients in the respiratory tree during HFOV 281
C) Role of prostaglandins in the pulmonary vascular response to HFOV in dogs 284
D) Lung clearance of radioactive particles 295
E) Use of a fixed-volume pump to ventilate small animals 304
F) Preliminary studies in dogs with oleic acid induced lung injury 307

Appendix I: Description and characterization of the HFOV system 312
Appendix II: Development of the body plethysmograph 332
Appendix III: Comparison of various plethysmographic methods for obtaining FRC in anesthetized dogs 339
Appendix IV: Changes in hemodynamics, lung mechanics gas exchange in dogs with saline-lavaged lungs 354
Appendix V: In vitro study of the effects of thermistor vibration on flow measurement by thermodilution 372
Appendix VI: Description of an inexpensive flowmeter for low-flow measurements 378

EPILOGUE 388

LIST OF TABLES

TABLE		PAGE
I-1	Miscellaneous HFV types	6
I-2	Confusions in the use of HFV terminology	8
I-3	Species used for *in vivo* animal studies	40
I-4	Pathologic lung models	41
I-5	Literature findings for PaO_2, $P(A-a)O_2$ and $PaCO_2$	50
I-6	Literature findings for $\dot{Q}s/\dot{Q}t$, HR, SAP and SVR	55
I-7	Literature findings for PAP, PVR, CVP and $\dot{Q}$	58
I-8	Reported uses of HFV in humans; FCV	68
I-9	Previous publications of HFV articles	74
1-1	Blood gas values obtained at different HFOV levels	146
1-2	Parameters calculated from blood gas and hemodydnamic data	147
1-3	Hemodynamic parameters obtained at different HFOV levels	148
1-4	Ppl and hemodynamic parameters corrected for transmural pressure	149
1-5	Parameteres calculated from hemodynamic data	150
1-6	Correlation of parameters with HFOV frequency	151
2-1	$\bar{P}aw$, Poc and calculated $\bar{P}alv$ during HFOV	166
3-1	Effect of HFOV, PEEP-V, PEEP-P and IPPV on hemodynamic parameters	182
3-2	Effect of HFOV, PEEP-V, PEEP-P and IPPV on blood gas parameters	183
3-3	Effect of HFOV, PEEP-V, PEEP-P and IPPV on RAP-IVCP and PWP-LVEDP gradients	183
4-1	Correlation of hemodynamic parameters with $\bar{V}_L$ and $\bar{P}d$	198
4-2	HFOV "compliance" and deflation Cst	199
4-3	Correlation of pairs of hemodynamic parameters	199
5-1	Differences between HFOV and PEEP after lung lavage	214
6-1	Baseline PaO_2 and $PaCO_2$ in Rcoll studies	235
6-2	Collateral ventilation parameters during HFOV and PEEP	235
7-1	General data for TMTR studies	250
7-2	TMTR of SB versus IPPV experiments	250
7-3	Effect of particle size on TMTR	251
7-4	Comparison of starting movements	251
7-5	TMTR of IPPV versus HFOV experiments	252

TABLE PAGE
8-1 Parameters obtained during BV, DV and PEEP 264
9C-1 Effect of IDM on the $\overline{\text{PAP}}$ response to HFOV 293
AIII-1 Individual TGV obtained by different methods 351
AIII-2 Statistical analysis of *in vitro* TGV data 351
AIV-1 Parameters obtained during IPPV and PEEP on lung lavage studies 364

LIST OF FIGURES

FIGURE		PAGE
Intro-1	HFV frequencies reported in the literature	4
1-1	Diagram of the HFOV circuit	152
1-2	Values for O_2 Del, PVR and Ppl during IPPV and HFOV	152
1-3	Values for $\overline{PAP}$, PWP and $\dot{Q}$ during IPPV and HFOV	153
2-1	Circuit used for ΔFRC measurements	167
2-2	Lung value and $\bar{P}$aw changes over time during HFOV	167
2-3	Effect of different HFOV levels on $\bar{P}$aw, $\bar{P}$pl and ΔFRC	168
3-1	Diagram of the HFOV-plethysmograph system	184
3-2	$\bar{P}$d changes during IPPV, HFOV, PEEP-V and PEEP-P	185
3-3	$\bar{V}_L$ changes during IPPV, HFOV, PEEP-V and PEEP-P	185
3-4	$\dot{Q}$ changes during IPPV, HFOV, PEEP-V and PEEP-P	186
3-5	O_2 Del changes during IPPV, HFOV, PEEP-V and PEEP-P	186
3-6	$\overline{PAP}$ changes during IPPV, HFOV, PEEP-V and PEEP-P	187
3-7	PVR changes during IPPV, HFOV, PEEP-V and PEEP-P	187
3-8	PWP changes during IPPV, HFOV, PEEP-V and PEEP-P	188
3-9	LVEDP changes during IPPV, HFOV, PEEP-V and PEEP-P	188
3-10	PWP minus LVEDP	189
3-11	IVC minus RAP	189
4-1	Diagram of the HFOV-pressure chamber-plethysmograph-spirometer system	200
4-2	Changes in $\bar{P}$d related to $\bar{V}_L$ variations	200
4-3	Changes in $\overline{PAP}$ related to $\bar{V}_L$ variations	201
4-4	Changes in $\overline{PAP}$ related to $\bar{P}$d variations	201
4-5	Changes in PWP related to $\bar{V}_L$ variations	202
4-6	Changes in PWP related to $\bar{P}$d variations	202
4-7	Changes in LVEDP related to $\bar{V}_L$ variations	203
4-8	Changes in LVEDP related to $\bar{P}$d variations	203
5-1	Changes in Cst during HFOV and PEEP after lung lavage	215
5-2	Changes in $\bar{P}$aw during HFOV and PEEP after lung lavage	215
5-3	Changes in $\bar{P}_L$ during HFOV and PEEP after lung lavage	216
5-4	Changes in $\bar{P}$eso during HFOV and PEEP after lung lavage	216
5-5	Changes in FRC during HFOV and PEEP after lung lavage	217
5-6	Changes in $\bar{V}_L$ during HFOV and PEEP after lung lavage	217

FIGURE PAGE

5-7 Changes in PaO_2 during HFOV and PEEP after lung lavage 218
5-8 Changes in $PaCO_2$ during HFOV and PEEP after lung lavage 218
5-9 Changes in $\overline{PAP}$ during HFOV and PEEP after lung lavage 219
5-10 Changes in PWP during HFOV and PEEP after lung lavage 219
6-1 Diagram of the ventilator-plethysmograph system for Rcoll measurements 236
6-2 Diagram of the catheter setup for Rcoll measurements 236
6-3 Rcoll of two dogs 237
6-4 P/V curves and $\overline{Pd}$ of two dogs 237
7-1 Dual-channel pipette for particle deposition 253
7-2 Diagram of the setup for TMTR measurement 253
7-3 Calculation of TMTR from radioactivity histograms 254
7-4 Change in TMTR after change from IPPV to HFOV 254
7-5 Circuit used to measure TMTR during SB and IPPV 255
7-6 Circuit used to measure TMTR during IPPV and HFOV 255
7-7 TMTR during SB and IPPV 256
7-8 TMTR durding HFOV and IPPV 256
8-1 $\overline{Pd}$ during BV/DV studies 265
8-2 ΔFRC during BV/DV studies 265
8-3 PaO_2 during BV/DV studies 266
8-4 $P(A-a)O_2$ during BV/DV studies 266
8-5 $\dot{Q}$ during BV/DV studies 267
8-6 O_2 Del during BV/DV studies 267
9A-1 $\overline{Pd}$ profiles from 8 dogs 279
9A-2 Average $\overline{Pd}$ values at different points in the airways 279
9A-3 $\overline{Pd}$ profiles at different frequencies 280
9A-4 $\overline{Pd}$ profiles with a retrograde catheter 280
9B-1 CO_2 gradients down the airways 283
9C-1 Circuit used for pressurizing the airway 294
9C-2 PAP changes over time after starting HFOV 294
9D-1 LCR dual probe, right versus left lung 301
9D-2 LCR dual probe first versus second h (right lung) 301
9D-3 LCR dual probe first versus second h (left lung) 302
9D-4 LCR multiprobe, right versus left lung 302
9D-5 LCR multiprobe, first versus second h (right lung) 303

FIGURE		PAGE
9D-6	LCR multiprobe, first versus second h (left lung)	303
9E-1	PaO_2 and $PaCO_2$ of two cats	306
9F-1	PaO_2, $PaCO_2$ and $\overline{SAP}$ in OA injury	310
AI-1	Diagram of the bellows pump	324
AI-2	Change in pump outlet air temperature	325
AI-3	Pressure delivered by the HFOV pump	325
AI-4	Tidal volume delivered by the HFOV pump	326
AI-5	Initial HFOV circuits	326
AI-6	Later-phase HFOV circuits	327
AI-7	Final HFOV circuit	328
AI-8	Effect of catheter size on V_T delivered	329
AI-9	Effect of chamber pressure on V_T delivered	329
AI-10	Effect of frequency on lung model pressure	330
AI-11	Change in lung model pressure with frequency during stable Palv	330
AI-12	Effect of bias flow on lung model pressure	331
AIII-1	Diagram of the plethysmograph	352
AIII-2	Diagram of the lung model setup	352
AIII-3	Helium dilution circuit	353
AIII-4	Lung model volumes measured by EC and PhN.	353
AIV-1	P/V curve of the esophageal balloon	365
AIV-2	P/V curves of a dog	365
AIV-3	Changes in Cst with lavage	366
AIV-4	Changes in $\overline{P}aw$ with lavage	366
AIV-5	Changes in $\overline{P}eso$ with lavage	367
AIV-6	Changes in $\overline{P}_L$ with lavage	367
AIV-7	Changes in PaO_2 with lavage	368
AIV-8	Changes in $P(A-a)O_2$ with lavage	368
AIV-9	Changes in $PacO_2$ with lavage	369
AIV-10	Changes in $\overline{PAP}$ with lavage	369
AIV-11	Changes in PWP with lavage	370
AIV-12	Changes in LVEDP with lavage	370
AIV-13	Changes in LVSP with lavage	371
AIV-14	Changes in PWP-LVEDP with lavage	371
AV-1	Effect of vibration on thermistor resistance	376

FIGURE		PAGE
AV-2	Circuit used for the *in vitro* $\dot{Q}$ tests	376
AV-3	Effect of vibration on *in vitro* $\dot{Q}$ measurements	377
AVI-1	Diagram of the flowmeter	343
AVI-2	Change in flowmeter's pressure at different air flows	343

ABBREVIATIONS

α	Angle of X/Y tracings
α cal	Angle of plethysmograph calibration tracings
apH	Arterial pH
ARDS	Adult respiratory distress syndrome
ARI	Acute respiratory insufficiency
b	Slope of the correlation line
BF	Bias flow
BPF	Bronchopleural fistula
BV	Bellows ventilator
bpm	Breaths per minute
$C(a-\bar{v})O_2$	Arterio-venous oxygen content difference
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
cpm	Counts per minute
CVP	Central venous pressure
Cs^1	Compliance of the occluded segment
Cst	Static compliance
$C\bar{v}O_2$	Oxygen content of mixed-venous blood
ΔFRC	Change in functional residual capacity
DV	Diaphragm ventilator
EC	External chest compression
EOV	External oscillatory ventilation
ETT	Endotracheal tube
f	Pump frequency
FCV	Fast conventional ventilation
FCal	Plethysmographic calibration factor
F_{IO_2}	Inspired oxygen concentration
FRC	Functional residual capacity
$[H^+]$	Hydrogen ion concentration
[Hb]	Hemoglobin concentration
h	Hour
HFJV	High-frequency jet ventilation
HFOV	High-frequency oscillatory ventilation
HFPPV	High-frequency positive-pressure ventilation

HFV	High-frequency ventilation
Hz	Hertz
I/E	Inspiratory/expiratory
ICP	Intracranial pressure
i.d.	Inside diameter
IDM	Indomethacin
IPPV	Intermittent positive-pressure ventilation
IRDS	Infant respiratory distress syndrome
i.v.	Intravenous
L	Litre
LAP	Left-atrial pressure
LCR	Lung clearance rate
LPF	Low-pass filter
LVEDP	Left-ventricular end-diastolic pressure
LVSP	Left-ventricular systolic pressure
LVSW	Left-ventricular stroke work
m	Meter
MCF	Mucociliary function
min	Minute
n	Number of items
o.d.	Outside diameter
O_2	Oxygen
O_2Del	Oxygen delivery
OAPE	Oleic acid induced pulmonary edema
$P(A-a)O_2$	Alveolo-arterial oxygen pressure difference
P_ACO_2	Partial pressure of carbon dioxide in the alveolar gas
$PaCO_2$	Partial pressure of carbon dioxide in the arterial blood
P_AO_2	Partial pressure of oxygen in the alveolar gas
PaO_2	Partial pressure of oxygen in the arterial blood
Palv	Alveolar pressure
$\bar{P}alv$	Mean alveolar pressure
PAP	Pulmonary artery pressure
$\overline{PAP}$	Mean pulmonary artery pressure
Paw	Airway pressure
$\bar{P}aw$	Mean airway pressure
Pawm	Minimal airway pressure

Pawp	Peak airway pressure
P_B	Barometric pressure
Pbox	Plethysmograph internal pressure
Pd	Distal airway pressure
$\overline{P}d$	Mean distal airway pressure
PEEP	Positive end-expiratory pressure
PEEP-P	PEEP ventilation at the same $\overline{P}d$ than during HFOV
PEEP-V	PEEP ventilation at the same end-expiratory lung volume than $\overline{V}_L$ during HFOV
Peso	Esophageal pressure
PG	Prostaglandin
P_{H_2O}	Partial pressure of water vapour
PhN	Phrenic nerve stimulation
P_L	Transpulmonary pressure
Poc	Airway occluded pressure
Ppl	Pleural pressure
Ps	Pressure in segmental airway
P/V	Pressure/volume
$P\bar{v}O_2$	Partial pressure of oxygen in the mixed-venous blood
PVR	Pulmonary vascular resistances
PWP	Pulmonary artery wedge pressure
PWP	Pulmonary artery wedge pressure
$\dot{Q}$	Cardiac output
$\dot{Q}s/\dot{Q}t$	Shunt fraction
r	Correlation coefficient
RVSW	Right-ventricular stroke work
Raw	Airway resistance
Rcoll	Colalteral resistance
s	Second
SAP	Systemic arterial pressure
$\overline{SAP}$	Mean systemic arterial pressure
SB	Spontaneous breathing
SD	Standard deviation
SHFV	Superimposed high-frequency ventilation
SV	Stroke volume

SVR	Systemic vascular resistances
SaO_2	Oxygen saturation of arterial blood
$S\bar{v}O_2$	Oxygen saturation of mixed-venous blood
$T\,{}^1/_2$	Time taken for counts to drop 50%
Tcoll	Time constant of collateral channels (corrected)
Tcoll'	Time constant of collateral channels (measured)
Tcr	Time constant of measuring system
TGV-EC	TGV measured during external chest compression
TGV-PhN	TGV measured during phrenic nerve stimulation
TGV-SB	TGV measured during spontaneous breathing
TM	Transmural pressure
TMTR	Tracheal mucous transport rate
Tt	Testing time
$\bar{v}pH$	Mixed-venous pH
$\dot{V}/\dot{Q}$	Ventilation/Perfusion ratio
$\dot{V}O_2$	Oxygen consumption
$\dot{V}coll$	Colalteral ventilation
$\bar{V}_L$	Mean lung volume
$\dot{V}min$	Minute ventilation
V_D/V_T	Dead space to tidal volume ratio
V_{Dan}	Anatomical dead space
V_{Dphys}	Physiological dead space
V_T	Tidal volume
Vent	Entrained volume
Vol	Lung model volume
Vs	Volume measured by the spirometer

FORMULAS USED TO CALCULATE HEMODYNAMIC AND BLOOD GAS PARAMETERS

$$\overline{\text{SAP}}\ (\text{mm Hg}) = \frac{\text{Systolic SAP} - \text{Diastolic SAP}}{3} + \text{Diastolic SAP}$$

$$\overline{\text{PAP}}\ (\text{mm Hg}) = \frac{\text{Systolic PAP} - \text{Diastolic PAP}}{3} + \text{Diastolic PAP}$$

$$\text{SVR}\ (\text{dynes} \times \text{s/cm}^5) = \frac{\text{SAP} - \text{CVP}}{\dot{Q}} \times 79.9$$

$$\text{PVR}\ (\text{dynes} \times \text{s/cm}^5) = \frac{\overline{\text{PAP}} - \text{PWP}}{\dot{Q}} \times 79.9$$

$$\text{SV}\ (\text{ml/beat}) = \frac{\dot{Q}}{\text{HR}}$$

$$\text{RVSW}\ (\text{g} \times \text{M}) = \text{SV} \times \overline{\text{PAP}} \times 0.0136$$

$$\text{LVSW}\ (\text{g} \times \text{M}) = \text{SV} \times \overline{\text{SAP}} \times 0.0136$$

$$\text{CaO}_2\ (\text{ml/100 ml}) = ([\text{Hb}] \times 1.39 \times \text{SaO}_2) + (\text{PaO}_2 \times 0.0031)$$

$$\text{C}\bar{\text{v}}\text{O}_2\ (\text{ml/100 ml}) = ([\text{Hb}] \times 1.39 \times \text{S}\bar{\text{v}}\text{O}_2) + (\text{P}\bar{\text{v}}\text{O}_2 \times 0.0031)$$

$$\text{C(a-}\bar{\text{v}}\text{)O}_2\ (\text{ml/100 ml}) = \text{CaO}_2 - \text{C}\bar{\text{v}}\text{O}_2$$

$$\dot{\text{V}}\,\text{O}_2\ (\text{ml/min}) = \dot{Q} \times \text{C(a-}\bar{\text{v}}\text{)O}_2 \times 10$$

$$\text{O}_2\text{Del}\ (\text{ml/min}) = \dot{Q} \times \text{CaO}_2$$

$$\text{PAO}_2\ (\text{torr}) = \text{F}_\text{i}\text{O}_2 \times [\text{P}_\text{B} - \text{P}_{\text{H}_2\text{O}}] - \frac{\text{PaCO}_2}{0.8} + \left(\text{PaCO}_2 \times \text{F}_\text{i}\text{O}_2 \times \frac{1 - 0.8}{0.8}\right)$$

$$\text{P(A-a)O}_2\ (\text{torr}) = \text{PAO}_2 - \text{PaO}_2$$

$$\dot{Q}\text{s}/\dot{Q}\text{t}\ (\%) = \frac{\text{P(A-a)O}_2 \times 0.031}{\text{C(a-}\bar{\text{v}}\text{)O}_2 + \text{P(A-a)O}_2} \times 100$$

The American Physiological Society

9650 ROCKVILLE PIKE
BETHESDA, MARYLAND 20814
TELEPHONE 301-530-7070

November 2, 1984

Dr. J. Armengol
Clinical Sciences Bldg., 6-106
University of Alberta
Department of Medicine
Edmonton, Alberta, Canada T6G 2G3

Dear Dr. Armengol:

You may use the information in your manuscript (A275-4), Collateral ventilation during high-frequency oscillation in dogs, which is scheduled for publication in the January 1985 issue of the Journal of Applied Physiology in your PhD thesis.

Sincerely,

Stephen R Geiger

Stephen R. Geiger
Publications Manager
and Executive Editor

SRG:lee

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INTRODUCTION

DEFINITION AND CLASSIFICATION

Definition

Although high-frequency ventilation (HFV) has been used for over 15 years, the definition of exactly what high frequency is remains unclear. There does, however, seem to be agreement that ventilation at rates above 60 breaths per min (bpm) can be considered to be HFV (565, 566). Slutsky et al. suggested that HFV be defined "as ventilation with frequencies at least 4 times greater than the normal value--about 60 breaths/min (1 Hz) in adults" (570). This agrees with the former statement for adults, but poses the problem of rejecting, for example, classical high-frequency positive-pressure ventilation (HFPPV) in neonatology (which sometimes uses rates of 60 bpm, Ref.678) because, to consider it as high frequency according to Slutsky et al, a rate above 144 bpm (4 x 34, Ref.801) would be required. Also, conventional ventilators have been used at rates up to 200 bpm (711) and manual ventilation up to 180 bpm (608). A recent publication has defined HFV as "... the term used to describe ventilation with volumes smaller than anatomic dead space" (512) but this leaves out many HFV reports (especially high-frequency jet ventilation and HFPPV) because they used tidal volumes (V_T) greater than dead space.

In this review, HFV is defined as ventilation at rates of 60 bpm and above, independent of the type of ventilator used or the subjects' spontaneous respiratory rate. This definition includes reports using conventional ventilators at high rates, because, although the specially designed high-frequency ventilators might be more effective (613), conventional ventilators induce similar physiologic changes when used at high frequencies (increased FRC and PaO_2, lower peak airway pressure;

see below under "Review of HFV research"). Fig.1 shows the maximal ventilator rates used in different experiments, arranged according to types of HFV.

In addition to rate, there is another basic difference between HFV and IPPV: it is well established that normal gas exchange can be achieved during HFV with V_T smaller than the physiological dead space (V_{Dphys}) but, although this is true for HFOV (323), it is not as clear for the other HFV types, because in them the actual V_T delivered to the airways is much more difficult to assess. Consequently, the use of a V_T smaller than V_{Dphys} cannot be used as a criterion to define HFV.

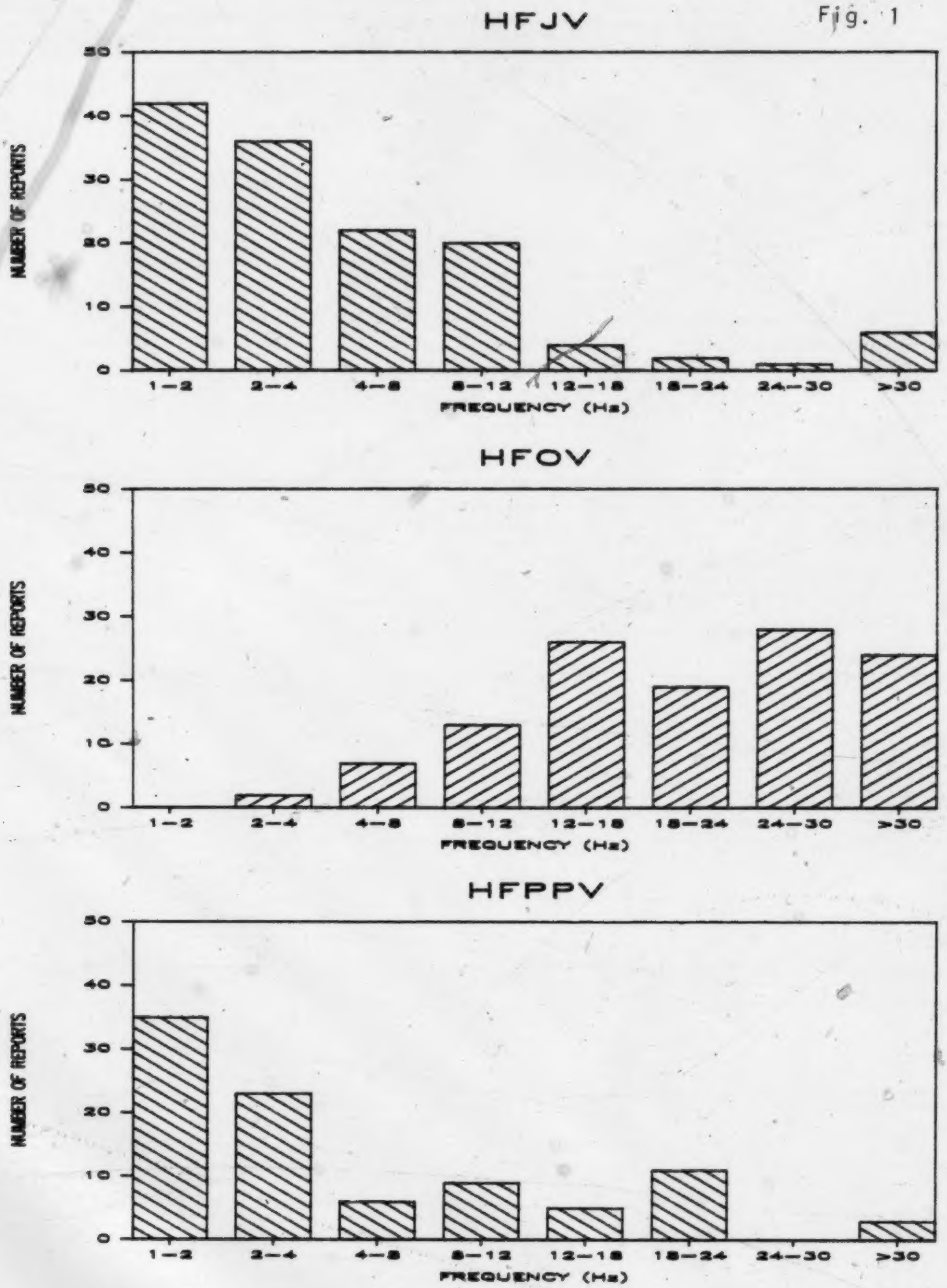
Types of high frequency ventilation

According to the technical characteristics of the ventilators and circuits used, HFV can be divided into five major types: a) jet ventilation; b) high-frequency positive-pressure ventilation (including fast conventional ventilation); c) high-frequency oscillatory ventilation; d) superimposed HFV; and e) external high-frequency oscillation.

High-frequency jet ventilation (HFJV): In this form of ventilation the tidal volume is delivered into the airway through a narrow-lumen canula (usually 14 to 18 gauge), either transtracheal (244) or attached to the endotracheal tube (43). The gases exit the canula at very high speeds (more than 500 m/s, calculated from Refs.43 and 55), creating a Venturi effect which entrains more gas, increasing the tidal volume delivered to the lungs. The usual rates vary between 100 and 600 bpm, although rates as high as 50 Hz have been attempted (13).

High-frequency positive-pressure ventilation (HFPPV): In this modality, the ventilator delivers the tidal volume directly into the

Fig. 1



HFJV

HFOV

HFPPV

Figure 1: Distribution of the maximal respiratory frequency used in publications describing experiments with the tree major HFV types.

endotracheal tube (720), without entraining gas (at least theoretically). The rates are usually somewhat slower than those of HFJV (60—200 bpm) although some groups have used rates up to 50 Hz (697). The velocity of the delivered gas is also slower (30 m/s, calculated from Ref.613). Fast conventional ventilation (FCV), has been included in this category; in it a regular intermittent positive-pressure respirator is used at high rates (classical HFPPV is delivered by special low compressible volume ventilators).

High-frequency oscillatory ventilation (HFOV): This form of ventilation induces an oscillating pressure wave at the airway opening, the airway pressure alternating between positive and negative, usually following a quasi-sinusoidal pattern (323). The rates commonly used are 5 to 30 Hz, although values as high as 60 Hz have been employed (333).

Superimposed high-frequency ventilation (SHFV): All of the previously-mentioned ventilation techniques have been superimposed on top of conventional ventilation, with some claimed advantages over the use of one ventilatory technique alone (see later).

External oscillatory ventilation (EOV): This modality is achieved by applying an oscillating pressure wave externally, either to the whole body (765) (the animal being enclosed in a sealed chamber) or to a localized part of the animal's chest (773). The frequencies applied vary between 1 and 45 Hz.

Other types of high-frequency ventilation: Several authors have described "new" methods of HFV, which produce a pressure wave similar to the above-mentioned categories by using a different ventilatory setup. Table 1 lists these methods, together with the category in which they were included and the author's acronym. A total of 15 different types

TABLE 1: Miscellaneous HFV types

Ventilation	Author's	Ventilation	Ref.
High-frequency alternating lung ventilation	HFALV	HFJV	108
High frequency pulsation	HFP	HFJV	275
Forced diffusion ventilation	FDV	HFJV	13
Combined high-frequency ventialtion	CHFV	HFJV	82,257
High-frequency jet oscillation	HFJD	HFJV	190
Digital ventilation	DV	HFPPV(HFOV)	279
Volumetric diffusion respiration	VDR	HFPPV(HFOV)	427,675
Pneumatic high frequency oscillation	PHFO	HFOV	319
Vibratory ventilation	VV	HFOV	321
Oscillated ventilation	--	HFOV	504
Vibratory positive end expiratory pressure ventilation	--	HFPPV	743
High frequency, low tidal volume ventilation	HF-LTV	HFPPV	689
Modified high frequency positive pressure ventilation	m-HFPPV	HFPPV	686
High frequency pulse ventilation	HFPV	HFPPV	688
Pulsatile assist ventilation	--	HFPPV	728

were found in the HFV literature.

Confusions about terminology: In several cases, a standard method is used which fits into one of the previous categories, but is described by the authors as another type. A total of 26 of these reports were identified in the HFV literature; they are summarized in Table 2. These confusing misuses of terminology were more common in early reports published as abstracts. In some cases, when publishing these abstracts as full papers, the proper terminology was used (for example Refs. 38 and 41 were first described as HFPPV and later published as HFJV in Ref.51). Usually the proper category can be defined by the methods described in the publication, and in other cases it can be deduced from more descriptive reports by the same authors. However, in some cases, it is difficult to decide the category of a particular method. For example HFPPV delivered through a narrow bronchoscope (631)—which probably induces a significant entrainment of gases—could be considered as HFJV, but this and similar cases were classified as HFPPV.

The criteria used to classify HFV, although widely used (554,556, 558,565,566,567,570) are by no means universally accepted. Some authors do not consider wave form or gas entrainment, and classify HFV only according to frequency, including for example HFPPV at rates between 110—400 bpm as HFJV, and both HFJV and HFPPV faster than 400 bpm are considered HFOV (571). Other authors do not differentiate between HFJV and HFPPV (573), and finally some neither consider waveform nor distinguish between HFJV and HFPPV (628).

TABLE 2: Confusions in the use of HFV terminology

HFV SYSTEM REPORTED	ACTUAL HFV SYSTEM	REFERENCE #
HFPPV	HFJV	37
HFPPV	HFJV	42
HFPPV	HFJV	81
HFOV	HFJV	82
HFPPV	HFJV	82
HFPPV	HFJV	83
HFOV	HFJV	130
HFPPV	HFJV	246
HFPPV	HFJV	260
HFPPV	HFOV	359
HFPV	HFOV	489
HFPPV	HFOV	490
HFPPV	HFOV	491
HFOV	HFPPV	573
HFPPV	HFJV	612
HFPPV	HFJV	628
HFPPV	HFJV	629
HFPPV	HFJV	630
HFPPV	HFJV	632
HFOV	HFPPV	650
HFOV	HFPPV	667
HFOV	HFPPV	671
HFPPV	HFJV	677
HFPPV	HFJV	690
HFJV	HFPPV	706
HFPPV	HFJV	724
HFOV	HFPPV	727

HISTORY

Basic concepts related to HFV

Although HFV is only 15 years old, several of the basic underlying concepts, like diffusion enhancement, the use of V_T's smaller than the anatomical dead space (V_{Dan}) and high respiratory rates, have been discussed for many years. The following observations can be considered relevant steps towards the understanding and development of HFV:

1) Loewy in 1891 described the presence of significant amounts of CO_2 in the gas coming from V_{Dan} (cited in Ref. 805).
2) In 1909 Meltzer and Auer described that a continuous flow of air in the airway could maintain an adequate PaO_2 in the apneic dog (833).
3) Henderson et al. in 1915 emphasized the nonuniformity of V_{Dan} and its importance in gas exchange, and postulated that high respiratory rates could maintain adequate ventilation with $V_T < V_{Dan}$ (822).
4) Draper and Whitehead reported in 1944 adequate PaO_2 in dogs, maintained by continues insuflation of O_2 into the airway, with what they called "diffusion respiration" (814).
5) Ross in 1957 reported some morphometric studies in the dog in which he found that some alveoli are situated quite close to the carina. He calculated that these alveoli could be adequately ventilated with V_T=V_{Dan} if respiratory rate was high enough (838).
6) In 1959, Altshuler et al. quantified the role of bulk transport in the intrapulmonary mixing of gases during tidal breathing. In a series of experiments with aerosol particles, they found that during tidal breathing, a substantial portion of V_T remains in the lung at end expiration, over several breaths (802).

7) As fluidic ventilators, based on the "Coanda effect", are commonly used in both HFJV and HFPPV, the history of their development will be briefly mentioned: In 1933 Coanda described the wall-attraction phenomenon in jets of fluids (Coanda effect), which was applied in fluidic controls by Horton et al. in 1959, and later by Warren and Staub (1964) in the first fluidic ventilators (564).

8) Before the development of HFJV, jet ventilation had been used transtracheally or during bronchoscopy at low rates. Transtracheal insuflation of a continuous flow of oxygen through a needle was first reported by Jacoby et al. in 1951 (125), the same group in 1953 reported adequate ventilation with the use of an intermittent (manual) jet of oxygen, applied transtracheally at a rate of 12—20 bpm in dogs (213), and in humans in 1956 (95). A respirator (Bird Mark II) used for transtracheal jet ventilation was first described in 1971 by Spoerel et al., using a rate of 12—16 bpm (253). The use of an intermittent jet for ventilation during bronchoscopy was first reported in men by Sanders in 1967 (220); the rate used was 20 bpm, maintained by manual interruption of the flow. In 1969 Spoerel described the use of a Bird Mark II respirator for jet ventilation during bronchoscopy (252); the rate used was 16 bpm.

9) A relevant step towards the development of EOV was the observation made by Johnson in 1972 that high levels of infrasound noise induced apnea in intubated dogs (mentioned in Ref.769). The use of infrasound for artificial respiration was suggested by Evans in 1976 (769).

Early uses of HFV

a) HFJV and HFPPV: The first publication describing the use of HFPPV appeared as an abstract in 1970, reported by a Swedish group (689); it was then called "high frequency, low tidal volume ventilation". The next year, an extensive description of the technique was published by the same group who called it, for the first time, HFPPV (690); the rate used was 60—100 bpm. In both of these studies and one which appeared in 1973 (677) ventilation was delivered through a catheter inserted down to the lower part of the endotracheal tube (ETT). Unfortunately, the diameter of this catheter is not mentioned, but from the drawings it appears similar to the ones later used for HFJV. Moreover, the design of the expiratory valve would not impede the entrainment of air into the circuit. Other authors have used HFJV at rates below 100 bpm (140), so it seems that the first reports on HFPPV could actually be classified as HFJV. In 1973, the same Swedish group published a report using a similar respirator on cats (691). In this case, no catheter was used, and the ventilator was connected directly to a tight-fitting ETT which should also minimize air entrainment. This could be considered as the first report on HFPPV. In a latter report, in 1976 (718), this group described a pneumatic HFPPV valve, which has been used by these researchers in most of their subsequent experiments with HFPPV (720).

The first "classical" HFJV report, was published by Klain and Smith in 1977 (140). They used a 14 gauge canula inserted transtracheally in dogs, with rates between 20 and 200 bpm; gas entrainment is not mentioned in the report. The first communication on the clinical use of HFJV appeared in 1978 as an abstract by the same group (141).

b) HFOV: In 1959, Emerson patented a device "for treating a patient by vibrating a column of gas which is in communication with his airway... [using] 100 to more than 1500 vibrations per minute...." (351). This, the first HFOV prototype (actually, superimposed-HFOV) was never fully applied or tested (572); further modifications of the system have been used only recently (394,441). In 1972, Lunkenheimer et al. reported in a letter to the Editor of the British Journal of Anaesthesia the use oscillation at high frequencies in dogs (409); a full paper was published the next year (410). In 1979, Dr. Bryan's group were the first in reporting the use of HFOV in humans (337).

c) SHFV: Although Emerson's 1959 oscillator was designed to deliver superimposed oscillation, the first reports of its use did not appear until 1983 (403,420); earlier uses were as conventional HFOV (441). In 1981 the first experiments were published describing superimposed HFJV (177), HFOV (427) and HFPPV (731).

d) EOV: In 1981, Ward et al. published their observations on gas exchange of isolated rat lungs oscillated externally at high frequencies (771). In 1982, Zidulka et al. reported the first in vivo EOV experiments in intact dogs (774). The first human studies were reported almost simultaneously by Irvin et al. (766) and Calverley et al. (762) in 1983.

TECHNICAL ASPECTS

The Ventilators

a) HFJV and HFPPV: These ventilatory techniques differ essentially only in the way the pressure wave is delivered into the airway. The ventilator consists of a more or less elaborated way of intermittently releasing gas from a high pressure source; actually, most of the prototypes could be used to deliver both HFJV and HFPPV (558).

Several interrupting systems have been used. Manual interruption has been reported only in slow jet ventilation either transtracheally (238), during laryngoscopy (200) or during bronchoscopy (242). A simple cam-operated mechanical interruptor has been described for HFJV use (60), but in order to vary the inspiratory/expiratory (I/E) ratio, the cam had to be changed. The most common ventilators use either a solenoid (44) or a fluidic (29) interrupting system. The solenoid allows a versatile control of rate, waveform and I/E ratio; a shut-off safety mechanism can be easily incorporated (720). However it has some disadvantages: the moving parts (electromagnetic valve) are subjected to wear (562), which may be hazardous to the patient (44), and are expensive (562). The fluidic system has no moving parts (29) that can wear: it is based on the deflection of a high velocity jet of gas by an intermittent gas stream, into either the patient circuit or the atmosphere. A comprehensive review of fluidic technology can be found in Ref.816. A third type of interrupting device that has been called "rotary valve" (646) or "rotating ball" (130), consists of a shaft or ball that turns at high speed (up to 40 Hz, Ref.681) and has a hole that connects the patient's airway alternatively to the high pressure source or to the atmosphere (646). Solenoid-type ventilators are used both in HFJV and HFPPV, while the fluidic type is mostly used in HFJV and rotary-valves are used in HFPPV. Several prototypes are commercially available: VS-600 (Instrument Development Corporation Laboratories, Pittsburg, PA) is a solenoid-type used in HFJV; Emerson 2-V (J.H. Emerson Co., Cambridge, MA) is a rotary-valve type used mainly in HFPPV; Bronchovent (Siemens-Elema AB, Solna, Sweden) is a solenoid-type used mostly in HFPPV; MK-800 (Instrument Development Corporation Laboratories, Pittsburg, PA) is a solenoid-type used in HFJV. Although it has been claimed (at least for HFPPV) that the use of a special ventilator with minimal compressible volume is mandatory (720), there are many reports on the use of conventional ventilators at high rates to deliver HFJV (for example, Refs.71,270) or HFPPV (for example, Refs.614, 640,698,705). There is little data in support of the hypothesis that such a special ventilator is better than a conventional one, modified to reach high respiratory rates (613,633).

b) HFOV: The HFOV respirators are more complicated mechanically because there are more and larger moving parts. The simplest model consists of a piston driven back and forth by an electrical motor through an eccentric cam (323) or a linear displacement motor (372). The major problem with this system is that if the piston is too tight, so as to reduce leaks, friction and wear become a problem, especially at high frequencies; a loose piston will have low friction but then the leaks become the problem. With motor-driven diaphragm oscillators (330,351), the major drawback is the wear of the membrane, not leaks or friction. All these problems can be obviated with a metal bellows oscillator (457) but so far only fixed stroke-volume systems are available. Another alternative is the use of a solenoid-driven diaphragm (411) or a loudspeaker (369); although these systems are very versatile in terms of changes in frequency, V_T or waveform, it is difficult to get large enough volume displacements at high frequencies (369), unless several speakers are used in parallel (478). HFOV has also been induced by connecting to the ETT alternating jets of air in opposite directions, parallel to the ETT axis (319).

c) SHFV: There have been several reports of superimposition of a jet on top of IPPV (3,29,191) and Siemens-Elema has its own prototype (186). There have been only two publications of superimposed HFPPV (728,731). Superimposed oscillation has also been attempted several times, with a piston pump (372), a diaphragm vibrator (420,504), a speaker (427), and a reciprocating jet (319).

d) EOV: Three types of oscillators have been applied for EOV: piston (773) diaphragm (770) and speaker (772).

The circuits

a) circuits for HFJV: The high-pressure gas is delivered into the airway through a narrow canula. This canula can be situated at many different levels: proximal ETT (43), tip of the ETT (60), somewhere between these two points (232), through the wall of the trachea (140) or the ETT (133), positioned below the vocal cords during endoscopy (242), inserted through a bronchoscope (221), placed in a major bronchi during bronchial surgery (81) etc. Some groups use catheters with side holes at the tip (83,245), which may help reduce trauma to the airway (254). There are ETT's available, with a jet catheter built into their wall, with the tip in the lower portion (249) or distal end of the ETT (4) and also with two catheters protruding from the ETT tip (180).

The high-speed jet entrains the gas proximal to it, augmenting the V_T delivered to the lungs (43); this effect probably decreases the closer the catheter tip is to the carina (558). The technical aspects of gas entrainment will be discussed in detail later. Due to the relationship between pressure, flow and resistance (Flow = Pressure difference/resistance; Ref.828), a higher driving pressure and larger catheter will cause an increased tidal volume; this has been supported by experimental data (55). It must be borne in mind that there could be a substantial pressure gradient in the circuit, between the high pressure source and the end of the catheter, mostly due to the resistance of the catheter (35).

The aerodynamic characteristics of the HFJV circuit may induce a PEEP effect of a few cm of H_2O (44,175) which can be increased further by partial obstruction of the expiratory circuit (232).

b) Circuits for HFPPV: Usually the outlet of the HFPPV respirator is connected directly to the endotube (646,652); sometimes a specially designed pneumatic valve is used, which can be modified to induce variable levels of PEEP (720).

c) Circuits for HFOV: The classical HFOV circuit (323) was shaped like a cross, with opposite arms connected one to the ETT and one to the oscillator. One of the remaining two arms, was connected to pressurized air (or O_2) and the other had a long tube that acted as a low pass filter (LPF) to allow CO_2 to escape. In recent experiments it was found that a fraction (which varied with frequency) of the V_T was lost in this circuit (338,421), probably through the LPF, but also perhaps through the pressurized air line. This problem was obviated with the use of high-impedance tubing and a vacuum source instead of an LPF (463,479) or alternatively with a closed-circuit design (441). In some systems the oscillation is delivered through a nozzle like in some HFPPV circuits (460,503). There are reports of HFOV delivered through a mouth piece, without intubation (369,437,487).

The range of bias flows (BF) used has been quite wide: from 0.2 L/kg/min (485) to 5.3 L/kg/min (421). Although higher BF improve CO_2

removal (394), large BF's may be unnecessary (485). It has been suggested that the closer the BF is to the carina, the better the CO_2 removal (362,466).

d) Circuits for EOV: There are two main approaches to EOV: a chamber that encloses the whole body (765) or a cuff wrapped around the chest, air-filled (773) or water-filled (761).

Other HFV types

There are a few reports that do not fit in the classical scheme outlined above. These are:

a) Pulsatile ventilation, obtained by inflating and deflating a balloon in an IPPV circuit (728); it has been considered as HFPPV, for the similarity in the pressure waveform.

b) Vibratory ventilation, generated by a special setup in a Servo ventilator (743); it has been classified as HFPPV because only positive pressure was generated.

c) Externally applied local or whole-body vibration (761), may be considered to be a form of EOV.

d) Alternating lung ventilation using a catheter in each major bronchus (108) can be categorized as HFJV.

e) Unilateral HFPPV with a catheter in a major bronchus (628) has been considered as HFJV because of the narrow catheter used.

Pressure waveform

a) HFJV and HFPPV: as the usual delivery systems are "on/off", in type, the ideal pressure wave ought to be square, but the compliance of the delivery system may dampen it, inducing a sawtooth-like shape; with this, end-expiratory pressure increases and peak airway pressure decreases (30,44). If the delivery system is not able to sustain a constant back pressure, a sawtooth-like shape might also result. Many reports include recordings of airway pressure, however the reliability of most measuring systems may not be optimal (see under "Measuring-pressures"). As frequency or I/E ratio increase, time available for emptying the lungs shortens and end-expiratory pressure rises creating a PEEP effect (17,30,175,649).

b) HFOV: The standard HFOV pressure wave has a quasi-sinusoidal shape (338) which can be generated mechanically by converting a circular motion into a straight displacement (836). Square flow waveforms have been tested but only in lung models (444,506).

c) EOV: If an oscillator is used, a quasi-sinusoidal pressure fluctuation can be expected. It is not clear what waveform will result from the variable leak in the systems in which EOV is delivered through a chest cuff (773).

Entrainment

A jet of gas at high velocity will induce a Venturi effect which will tend to entrain surrounding gases increasing the actual volume delivered (43). This entrainment depends on the velocity of the jet and will increase with higher driving pressures and narrower canula sizes (58). The fraction of entrainment volume may be substantially larger than the jet volume (2.6 times in Ref.73) and, as mentioned earlier, the closer the jet is to the carina, the smaller the entrained volume (558). An increased impedance of the respiratory system (decreased compliance or increased airway resistance) will decrease the entrainment and consequently the V_T actually delivered (71,175); this could be detrimental for patients who, for example, develop bronchospasm, because minute ventilation might be substantially reduced. A shorter I/E ratio and higher PEEP will also reduce the amount of entrainment (43,216).

Theoretically entrainment will occur only during HFJV, and HFPPV circuits are designed to avoid it (625); however, whenever fast HFPPV rates are used, together with ETT's narrower than the trachea, it may be expected that gas in the upper trachea is entrained and mixed with the V_T. Also during larynscopic or bronchoscopic HFPPV, entrainment of gases in the upper airways seems quite likely. Some HFOV systems that deliver the V_T through a nozzle (319,460,503) could also be expected to induce some gas entrainment. There are two main reasons why it is important to control and monitor entrainment: if it fluctuates, minute ventilation will fluctuate too (55); also, if a high FiO_2 is used, the entrained air will decrease oxygen concentration (98). Most HFJV circuits include a continuous flow of gas with known F_{IO_2}, in the expiratory port, to prevent changes in F_{IO_2} (43,232); some have valves to diminish rebreathing (269).

Conditioning inspired gases

During HFOV, it can be postulated that the to-and-fro gas movement induces a substantial amount of rebreathing, that is, part of the V_T is warm saturated air. However during HFJV and HFPPV, this rebreathing will be much less important, and due only to dead space ventilation. Also, the large minute ventilation generated by HFV can be expected to place an important stress on the "air-conditioning" mechanisms of the respiratory tract. Thus it seems of paramount importance, at least in HFJV and HFPPV, to deliver a gas that is warmed and humidified to avoid damage to the respiratory tract mucosa. Indeed there are many reports of mucosal damage when insufficiently conditioned gas has been used during HFV (29,43,137,151,211). Low humidity may also cause thickening of airway secretions with a tendency to plug the bronchi; this has been reported several times, especially in newborns (169,205,717). Mucociliary transport may also be impaired by a low-humidity jet (151). The cooling effect of a stream of gas at high velocity (831) on the airway can decrease core temperature; this has been reported several times both in for HFJV and HFOV (29,245,336). In order to avoid these problems, the gas delivered to the ventilator during HFV must be warmed and saturated with water; moreover, the gas flowing through the entrainment HFJV circuit must also be conditioned, which is usually done with a standard warmer-humidifier (232).

To warm-up the gas in the pressurized lines, a specially designed warmer that can withstand high pressures can be used (64). However, humidification of the jet during HFJV is usually accomplished by a needle positioned near the tip of the jet catheter, receiving a constant flow of saline from an infusion pump (44); the Venturi effect created by the jet of gas, nebulizes the saline into the airways. Some authors inject the saline directly into the ventilator catheter (232). As has been mentioned above, dry air damages the airways, but too much water may also be detrimental (188). There are special circuits designed for conditioning the gas during HFPPV (720); the bias flow in HFOV has also been warmed and humidified in some studies (429).

Safety

HFV uses a large volume of gas, and respiratory rates are high, so anything that prevents gases from escaping out of the respiratory system may pose a serious threat of barotrauma. There have been several reports of excessive intrapulmonary pressure, usually due to valve mechanisms created in the upper airways and ventilatory circuit during HFJV (29,193,232,265). In order to prevent the airway pressure from reaching dangerous levels, most commercially available high-frequency ventilators have a safety system that interrupts the flow of gas or vents the circuit to the atmosphere whenever airway pessure reaches a preset limit (175,260,371,720). Other potential technical problems of HFV include: a partial or total failure of the cycling mechanism which could cause hypoventilation; overheating of the ventilator (especially HFOV); leaks or disconnection of the respiratory circuit (260); failure in the oxygen mixing device, with a drop in F_{IO_2}; occlusion of the delivering circuit; introduction of particulate material in the airways due to mechanical wear of the ventilator (44); failure of the humidification system, especially with addition of excessive amounts of water. As experience with HFV increases, more accidents are expected to happen and the potential problems will be better defined. In the mean time, any system used for HFV must include a comprehensive fail-safe mechanism (572) especially when it is intended for clinical use.

Measuring ventilatory volumes during HFV

The important volumes to be measured are: tidal volume (V_T), minute ventilation volume ($\dot{V}min$), and entrainment (Vent). Although it has been established that HFOV can achieve gas exchange with $V_T \ll V_{Dan}$ (323,572), the actual V_T delivered in many experiments with HFJV might have been equal or larger than V_{Dan} (572).

a) HFJV: (1) V_T: There are two V_T's to be considered, the volume delivered by the ventilator and the volume reaching the airways. During HFJV, due to gas entrainment, the V_T reaching the lung is larger than the V_T delivered by the respirator. The ventilator-delivered volume is usually calculated in a bench study by connecting the jet canula to a spirometer (120). Impedance of the respiratory system should not affect these volumes significantly because airway pressures are much lower than ventilator driving pressures. A high-pressure flow meter could be inserted in the ventilator circuit, but this has not been reported. The ventilator volume could also be calculated by subtracting the volume going into the entrainment circuit from the volume coming out of it, and dividing by respiratory rate; this has not been reported either.

The actual ventilating volume is the sum of ventilator volume and entrainment. It could be assessed by plethysmography (body box, impedance, magnetometers) or by mesuring the exhaled volume with a flowmeter or spirometer. This latter method will be inaccurate if there is some entrainment of exhaled volume (rebreathing) which may be technically difficult to avoid.

(2) $\dot{V}$min: The ventilator volume may be obtained by multiplying V_T by rate; actual ventilating volume can be measured directly in the expiratory line, but keeping in mind the previously-mentioned rebreathing problem.

(3) Vent: This is obtained by subtracting the ventilator-delivered volume from the expired volume.

b) HFPPV: In this case, the ventilator volume may be larger than the volume reaching the airways, because some volume may be lost through the expiratory port; this may be more important when using a pneumatic valve

(720) bronchoscope (719) or laryngoscope (612). Entrainment should be considered when using a delivery system substantially narrower than the trachea, and high respiratory rates.

The volumes in HFPPV can be measured with techniques similar to what has been mentioned for HFJV.

c) HFOV: In this case also, part of the volume delivered by the ventilator can be lost (through the LPF and BF) and only a fraction reaches the airways; it has been estimated that up to half or two thirds of the ventilator volume may be lost (338). Some systems obviate this problem by using high-impedance (479) or closed (441) circuits; but even in these, part of the V_T may not reach the airways due to compression or resistance in the tubing (363). The ventilator V_T can be estimated by water displacement or measured with a pneumotachograph; actual delivered volume could be measured by plethysmography (320,441) if adequate corrections for frequency response are introduced.

d) EOV: The pressure change applied around the lung must overcome the impedance of the chest wall, lung parenchyma and airways; thus, exhaled volume will be only a fraction of the delivered volume (also part of this delivered volume is lost in the compression volume of the chamber or cuff). Delivered volume can be assessed by pressure/volume calibration of the chamber (or cuff) at different frequencies. Expired volume can be measured at the airway opening with a pneumotachograph (773) or a closed chamber acting as a plethysmograph (765).

Accuracy of the volume measurements:

Measurements of volume during HFV can be quite inaccurate if the frequency response and aerodynamic characteristics of the measuring system are not taken into account. Unfortunately, too often these factors are not considered and numbers are produced that have little meaning (361).

a) Rotameters: They may be used in high-pressure lines to assess ventilator volume or BF. They can only measure steady flows, and correction factors have to be introduced to correct for pressure-induced changes in gas density (832).

b) Anemometers: They have been used mostly to measure total exhaled volume, during HFJV (72,82,232) and HFPPV (610), but also to measure V_T (489,491). However, their frequency response is poor (813): the inertia of the moving parts causes underestimation of sudden increases in flow and overestimation of abrupt decreases. Correction for these errors has not been mentioned in any of the reports using anemometers.

c) Pneumotachographs: The Fleish and screen types have been used often in HFV, but their calibration may not have been always correct. One group used a pneumotachograph during HFPPV which had been calibrated only with a continuous flow of gas (613,632); this probably resulted in under-estimation of the volumes measured. When a fluid moves through a pipe, the molecules at the center tend to move faster than the peripheral ones (827); if a pneumotach is connected to this pipe, the pressure at its central part will tend to be slightly higher than at the periphery, this effect being more pronounced at higher gas speeds. Thus, when calibrating a pneumotach, it is important to keep flow profiles similar to what would be expected during experimental conditions; the relevant parts of the circuit have to be analogous in both conditions. Zidulka et al. (773) calibrated their pneumotachograph by attaching it to a 4-litre bottle and injecting volumes up to 100 ml into it. With Boyle's law (826), it can be calculated that during calibration, the pressure in the bottle would have reached pressures of more than 20 cm H_2O, which could be expected to alter significantly the flow profiles through the pneumotachograph, inducing erroneous calibration values. Other authors do not mention the calibration procedures or frequency response of the pneumotachographs used (58,75, 463,610,678,693).

d) Water spirometers: They have been used in several studies (60,219, 625,647) and can be considered one of the best standards, provided corrections for changes in temperature are made (which can be difficult when mixtures of fresh gas flow and expired gases are measured).

e) Plethysmographs and magnetometers: The electronic systems (inductive plethysmography and magnetometers) have a good frequency response (840) and have been used repeatedly, especially the inductive plethysmographs, to monitor volume changes during HFV (30,301,313,468); however diaphragmatic displacement and asynchronic lung expansion (408) may induce some error in V_T measurements. Volume body plethysmographs have a low frequency response and are not useful (848); pressure plethysmographs (441,512), with adequate correction for frequency response, may be the method of choice to estimate the V_T delivered to the lungs.

f) Testing the frequency response of the volume-measuring systems: Even if the measuring system does not have a flat frequency response up to the desired frequency, accurate measurements can be obtained with the use of correcting factors (479). To obtain these factors, the system is tested over a range of frequencies with a known volume oscillation, delivered by a dependable piston pump (479) or a more sophisticated speaker chamber (825).

Measuring resting lung volume during HFV

a) Changes in resting lung volume: The variations in FRC induced by HFV have been assessed with a body plethysmograph (225,402,513,714), impedance plethysmograph (468) spirometer (92,219,460,605), flowmeter (649) and Wright anemometer (345). All these methods seem to be reasonably accurate, with the exception of the Wright anemometer because the peak expiratory flows might be too high to be measured accurately by this turbine device (813).

b) Functional residual capacity: During HFV, there is usually an increase in FRC (457), which tends to inhibit respiratory center output through a vagally-mediated reflex (810); this phenomenon hampers the determination of FRC with the plethysmographic method of DuBois (815) which requires spontaneous respiratory efforts. There are no reports in the literature (other than Ref.309, described in this thesis) of plethysmographic FRC measurements during HFV.

The closed-circuit dilution methods are also impractical because most HFV systems are open; there are only two reports with a closed HFOV (414) and HFPPV system (708) that allowed FRC measurement by helium dilution. The only other direct methods of FRC measurement are based on gas washout, which involve more assumptions and are less reliable than the previously-described techniques (808). In spite of this most of the FRC measurements during HFV have been obtained with the washout methods, using: helium (340), nitrogen (202,636,694), ethane (334) or xenon (639).

Measuring airway and alveolar pressures during HFV

Most of the reports on HFV include measurements of airway pressures (Paw), however, in many of them the method used can be expected to give unreliable values. The airway pressures usually reported are: peak (Pawp), minimal (Pawm), and $\overline{P}$aw. Pawp and Pawm are read off the tracings and $\overline{P}$aw obtained by electronically averaging or mechanically damping Paw. Pawp and Pawm are measured at the tracheal level, and at high frequencies they may not reflect pressures in smaller airways or alveoli (and it is there that pressures are physiologically meaningful): due to the effects of airway resistance (Raw), Pawp may be expected to overestimate, and Pawm to underestimate, the pressures further down the respiratory tree.

$\overline{P}$aw has been used throughout to compare HFV and IPPV, with the assumption that it is a good estimate of mean alveolar pressure ($\overline{P}$alv). However, many authors have suggested that HFV creates a pressure gradient down the respiratory tree, with $\overline{P}$aw being smaller than $\overline{P}$alv (17,207,305,330,441,460,467,468,492,555,647).

In addition to these considerations there are some technical aspects of the measurements that have to be taken into account:

a) Measuring site: The previously-mentioned $\overline{P}$aw gradient, together with the reported decrease in pressure amplitude inside the ventilatory circuit and ETT (175,363,421,632), make it critical to take into account the site of pressure measurement when comparing Paw values from different reports. The locations used to measure Paw have varied greatly between groups: proximal to the ETT (205,328,645), inside (155,328,677), at the tip (231,430,742), several centimeters distal to the tip (92,342,658,664), transtracheally (245,328), at the carina

(82,503,741) or in the bronchi (441,641).

b) Frequency response: Whenever Paw is measured in the distal ETT or in the airways, a sampling catheter is used. If this catheter is too narrow (and/or long), its frequency response will be poor (836) but a large catheter will decrease significantly the lumen of the ETT and induce a change in Paw; a balance has to be achieved between the optimal frequency response and the catheter diameter. To accurately measure an oscillating frequency wave, the frequency response of the system has to be flat to at least 10 times the frequency of the oscillating pressure (835). It seems quite difficult to get accurate measurements of intratracheal pressure at frequencies above 10 Hz. Changes in internal diameter along the measuring system will also decrease its frequency response (819); it has to be kept as even as possible. A way to improve the frequency response is by filling the system with water (835), which has been done in several studies (43,231,734); however, the catheter has to be checked repeatedly for the presence of air bubbles which would decrease the frequency response (835). To test frequency response, the whole measuring system has to be checked with a sinusoidal pressure wave of varying frequency, against a reliable standard (825). An alternate method consists of measuring the frequency of the overshoot oscillations when measuring a square pressure wave (835). Some authors have used aneroid manometers, which have a poor frequency response (804), to measure airway pressures (690). Obviously, to measure $\overline{\text{P}}$aw a good frequency response is not necessary.

c) The catheter tip: If the gas molecules which are travelling at high speed close to the measuring catheter and parallel to it, suddenly reach its distal end, they will tend to follow a straight line, creating a relative vacuum around the catheter tip, which will be measured as a drop in pressure (809). This effect will tend to underestimate Pawp and $\overline{\mathrm{P}}$aw. Unfortunately end-hole sampling catheters have been used by many authors even during HFJV (where very high gas velocities are present), and their values (especially Pawp) may be erroneously low (30,136,199,231,232). One way to overcome this problem is to use a transducer-tip catheter (328,444). Another and cheaper method to elude this effect is to use a catheter with several side holes in its distal end (803); a few authors have used this approach (302,334,336,399,452).

d) Estimating $\overline{\mathrm{P}}$alv: There are a few authors that have attempted to estimate $\overline{\mathrm{P}}$alv. The method used was to clamp the airway during HFV and assume that the pressure after occlusion (Poc) equals alveolar pressure (219,330,468,476,645). This method may underestimate $\overline{\mathrm{P}}$alv due to the previously-mentioned airway pressure gradient created by HFV: if proximal $\overline{\mathrm{P}}$aw is lower than $\overline{\mathrm{P}}$alv, the equilibrium pressure (Poc) will be somewhere between the two. Also some of the alveolar volume may be used to distend airways that had inside pressures below $\overline{\mathrm{P}}$alv before clamping, further decreasing Poc.

MECHANISMS OF GAS EXCHANGE DURING HFV

It is still not clear how HFV achieves gas exchange with a V_T smaller than V_{Dan}. Three main theories have been put forward to explain it: gas convection, enhanced diffusion, and convection and diffusion combined. Of the publications that discussed any of the theories, the percentage in favour of each was distributed as follows: 28% convection, 21% diffusion and 51% both. It is interesting to note that the majority of experiments on the theoretical basis of HFV have been done with HFOV; perhaps it is because it allows better control of the variables.

Convection

There are several factors, based in gas convection, that may help explain how gas exchange can be achieved with $V_T < V_{Dan}$.

a) Interregional gas exchange: It has been postulated that since different lung regions have different time constants, during high frequency they would move out of phase and a fraction of volume would be transfered between adjacent lung regions (457). There is some experimental data to support this theory: when observing an excised lung under a strobe light, its surface can be seen to expand unevenly (406), and adjacent lung regions can be completely out of phase (408); also intraparenchymal lung markers have been found to move out of phase during HFV (375). There is a report of experiments with isolated rabbit lungs in which the phase differences between Palv in different lung regions was minimal (314), but the conditions of the experiments were not very physiological and may have interfered with the results; in another report, the same group found large phase differences in Palv of isolated dog lungs (395). This interregional gas transport—called "pendelluft" by some authors (361,457,555,572)—could increase the efficiency of a given V_T because part of it would be used over several respiratory cycles to ventilate different lung regions.

b) Different inspiratory/expiratory flow profiles: When a reciprocating flow is applied to a fluid inside a pipe for several cycles, the central molecules are moved forward and the peripheral ones backward (558,821). Experiments in branching models of the airways have shown that in addition to the reciprocating effect, the assymetry in inspiratory/expiratory flow profiles induces a further mixing of the inspired volume with the gas in the airways (572,821,834,842). This effect increases at higher flows, and although during spontaneous breathing it may only be important in large airways, during HFV it could reach the small airways (806) due to the increased local flow rates. It has been estimated that during spontaneous breathing, between 10 and 30% of the V_T remains in the lung at end-expiration, mainly due to bulk transport (802) and this facilitates gas transport in the airways.

c) Short bronchial path length: In 1915, Henderson et al. (822) observed the presence of CO_2 in expired gas coming from V_{Dan} and postulated the possibility of ventilation with $V_T < V_{Dan}$. Later, Ross (838) described his morphometric studies in a plastic cast of the airways, in which he found that some alveoli were situated quite close to the carina; his calculations suggested that these alveoli could maintain gas exchange with $V_T = V_{Dan}$ at high respiratory rates, because as frequency increases they contribute more and more to total alveolar ventilation.

d) Studies supporting that convection is the main gas exchange mechanism during HFV: Besides the above-mentioned reports on interregional gas movement (375,406,408), other experimental results during HFV support that convection is important in gas exchange during

HFV. Gas transport and exchange have been found to be determined by convective parameters in lung models (379,444), dogs (342,378), and humans (735); gas movement was independent of gas density or molecular weight in dogs (378,398,399,430,470) and geese (447); aerosol reaches the alveolar region even with $V_T < V_{Dan}$ (416,505); branching increases convective gas transport in dogs (434); and HFV induces a fluctuation in airway diameter in phase with the respiratory cycle (209).

Diffusion

During HFV, some processes may enhance or facilitate spontaneous diffusion of respiratory gases to such an extent as to allow normal oxygenation and ventilation.

a) Oscillatory flow: Experiments with simple linear models show that an oscillating movement greatly enhances spontaneous diffusion of molecules (385,807,837).

b) Cardiogenic mixing: The transmission of the heart beat to the respiratory system can increase intrapulmonary gas mixing more than five fold (820).

c) Taylor's dispersion: When a soluble material is added to a pipe through which a fluid is moving with laminar flow, dispersion in the fluid is increased proportionally to the square of the fluid velocity (Taylor's diffusivity, Ref.844); if the flow is turbulent, the dispersion is proportional to the velocity of the fluid (845). If the flow (unidirectional) is through a branching network, diffusion is several thousand times higher than if it was due to spontaneous molecular movement (841), at a range of fluid velocities similar to those found during HFV (323).

d) Studies supporting that diffusion is the main gas exchange mechanism during HFV: The following HFV experimental data have been used as evidence favouring enhanced diffusion as responsible for gas exchange during HFV: Washout of gas from the lung was found to be dependent on gas density (350,357); gas transport was not changed by partial airway occlusion (699) or regional time constants (727); changes in bias flow did not alter the shape of CO_2 gradients in the airways (394); gas transport was mainly dependent on frequency and/or flow in intact dogs (110,426,486,512), isolated dog lobes (407) or lung models (385,405). Also analysis of theoretical diffusion-enhancement equations can explain gas exchange (334,818).

Diffusion plus convection

It is puzzling to have so much evidence favouring two opposite theories; however, a careful analysis of the data may prove that there is not much contradiction. For example, some facts supporting convection, like interregional gas movement, aerosol transport and effect of branching, do not exclude the presence of diffusion, because it could take place in addition to convection. The same is true for some diffusion reports, like the theoretical analysis, CO_2 gradients, airway occlusion and independence from regional time constants (in the two later cases interregional mixing, for example, could decrease uneveness of gas distribution). The dependence of gas transport on V_T is one of the determinants of convection, but it could also be related to enhanced diffusion because an increase in V_T would create higher linear velocity which is an important factor in diffusion enhancement (818). The same velocity could be achieved with high V_T at low frequency and with low V_T at high rates but it seems that part of the V_T is necessary to washout the circuit dead space by convection (396,479); moreover, a portion of a large V_T (creating high airway pressures) may be lost in distension of the airways (464). These effects combined, together with the differences in circuits used (with varying degrees of effectiveness), and methods of measurement (see before, under "Technical aspects") might be responsible for the discrepancies in the results obtained by different groups.

The disagreement in the effects of varying gas density (or molecular weight) may also be related to technical problems: the studies that found no effect (and supported the convection theory) used 1% (or less) of foreign gas concentration; the reports that found dependence on gas density used gas concentrations of 80%. Thus it seems that 1% of foreign gas was not enough to induce changes large enough to be detected.

In conclusion, there is enough evidence to support the presence of both convection and enhanced diffusion mechanisms during HFV. Also, although there are many studies supporting one or the other, there is no clear evidence against the presence of either. So it can be concluded, like many authors (473,487,555,558,567 568,572,573), that gas exchange during HFV is based both in convection and enhanced-diffusion mechanisms. Slutsky et al. have divided the lung in 3 zones: zone I, including alveoli and small airways (up to 0.2—0.5 mm in diameter) where flow rates approach zero; zone III includes large airways, with turbulent flow and swirling of streamlines at bifurcations; zone II, the region between I and III, with flows mainly laminar. In zone I gas mixing is mainly due to molecular diffusion; in zones II and III, gas transport is accomplished by the combined effects of bulk flow and augmented diffusion (480,572). The larger the V_T, specially if it is larger than V_{Dan}, the more important convection becomes, and zone II extends more to the periphery.

REVIEW OF RESEARCH ON HFV

Foreword

This review of research includes data obtained from a total of 727 HFV-related publications, mostly full articles and abstracts, but also some editorial reviews and letters to the editor that contained relevant data not reported elsewhere. From these, a total of 130 articles, mostly abstracts, were considered as repeated information, usually included in latter reports as full articles (see later under "The HFV literature"), consequently their information is not mentioned in this review. It was felt that because many articles are aimed at proving how good HFV is, stress had to be put on negative findings, even though in several instances they did not reach statistical significance (usually due to small sample size or large scatter of data). Also, when a report had both a positive and a negative finding in regard to a measured variable, the negative one was stressed in this review. A distinction was made between articles showing no significant change in the parameter discussed (HFV values similar to control levels) and articles showing a "non-significant" increase or decrease (HFOV values different to control levels, but statistical significance not reached due to small sample size or large SD). There are several contradictory reports, which may be due in part (as will be discussed later) to the diversity of HFV circuits used (361). Because of the large amount of data available a rather global approach was attempted. Data on technical aspects and complications of HFJV, is scarce; some of this information was obtained from articles using low frequency jet ventilation. To keep the text simple, large groups of references are listed in tables throughout the text.

Theoretical Studies

These include reports on mathematical analysis of HFV-related physics and on electrical models of parts of the respiratory system during HFV.

a) HFV-related Physics: Theoretical analysis of HFV-related aspects have been reported in the following fields: factors influencing diffusion and convection of gases (334,468,478,480), parameters of CO_2 removal from the alveoli (380,396,446,715), and pressures in airways and alveoli (330,355,493).

b) Electrical models: An electrical model has been used to analyze the following topics: CO_2 elimination (464), effect of a broncho-pleural fistula on ventilation (212), pressures and flows of a lung-ventilator system (555,646), and PEEP effect at the alveolar level (645).

In vitro experiments

Two types of *in vitro* studies have been reported: lung models and isolated lungs.

a) Lung-model experiments: The effects of HFV have been reported in experiments with lung models. The following systems have been used: single tubes (64,312,385,392,405,430,436,446,487), cones (461), bottles (186,240,444,646), and branching networks of tubes (16,303,344,385,476, 817,834,843). These models have been mainly used to study gas transport or the convection and diffusion mechanisms described earlier. Two studies with branching tubes (303,476) have also studied the gradients in airway pressure created by HFV; one of them (476) concluded that HFV induces a $\overline{P}alv$ significantly higher than proximal $\overline{P}aw$. More-conventional balloon-type models have also been used to test endotracheal tubes (249,327), ventilators (72,614,615,617) or circuits (73,178,282).

b) Isolated lung experiments: The following HFV experiments have been done with isolated lungs:

- Lehr in 1980 described uneven movement of the surface of dog lungs during HFOV (406); two years later, Lehr et al. quantitated the phase lag of different lung segments (408).
- Valber and Sneddon studied the deposition of aerosol in dog's lungs during HFOV (505); they found that even with a small V_T, the aerosol reached peripheral lung regions at the same speed as O_2 did. They suggested a mainly convective mechanism of gas transport.
- Lehr et al. sampled tracer gas at different levels of dog airways during HFOV and concluded that there was a fast-turnover proximal space, and a peripheral slow one (407).
- Toung et al. using acid-lavaged dog lungs concluded that HFOV and IPPV induced the same lung water content (501).
- Mautone et al. were able to ventilate immature lamb lungs with airway pressures lower during HFOV than during IPPV (423).
- Allen et al. directly measured Palv in rabbit lungs during HFOV and found that at certain frequencies (resonant) the Palv oscillations were larger than the oscillations in Paw; there was minimal asynchrony between different measuring sites (314). The same group found similar Palv oscillations in dog lungs but with marked asynchrony between regions (395). It is not clear if the differences were due to species differences or to an artifact of the methods used.
- Berdine et al. found that the washout of ethane from dog lungs during HFOV was dependent on frequency and V_T (320).

- Boynton et al. described a method to overcome the inaccuracy of pressure measurement through a multi-lumen catheter, as compared to a direct measurement, in the tracheas of rabbits (328).
- Gordon et al. studied isolated sheep lungs during hypoxia and concluded that prostacyclin release, induced by HFPPV, causes a blunted hypoxic pulmonary vasoconstrictor response (666).
- Ward et al. were able to achieve good oxygenation of blood flowing through isolated rat lungs ventilated by EOV (772).

In vivo experiments: animal studies

I. - Species: The species most commonly used for HFV studies has been the dog, (Table 3) the next most common species have been the rabbit and the cat. Other animals were used less often, like sheep, monkeys, rats, pigs, horses, geese, ducks, and chicken. Most of the animals used were adults, only 9 studies used newborns (315,321,343,423,449,714,717,720, 732) and 7 used prematures (36,316,348,442,483,503,602,603).

II. - Pathologic lung models: There are 77 reports of HFV studies on abnormal lungs, (Table 4) the most common model being oleic-acid induced pulmonary edema (OAPE) with 20 reports in dogs and 3 in rabbits. There are 10 reports of saline-lavaged lungs: in rabbits, dogs and in cats; eight reports of immature lungs of monkeys and lambs; seven reports of open-chest animals in dogs and cats; and 7 reports of bronchospasm (or mechanical airway obstruction) in dogs. Other models were used less frequently, like air embolism, meconium aspiration, bronchopleural fistula, tracheal fistula, hydrochloric-acid aspiration, hydrochloric-acid aspiration plus OAPE, BPF plus OAPE, hemorrhagic shock, neurogenic pulmonary edema, alloxan-induced pulmonary edema, and OAPE with open chests.

TABLE 3: Species used for in vivo animal studies

Species	Ventilation	Number	References
Dog	HFJV	61	8,5,10,11,23,30,33,48,55,57,58,60, 64,65,66,67,68,78,79,90,108,119, 133,134,136,140,150,151,155,157, 163,173,174,181,184,188,190,191, 199,201,202,209,210,223,225,231, 244,245,255,256,260,261,263,264, 277,282,348,381,382,387,625.
Dog	HFOV	72	304,306,307,308,309,313,323,329, 330,333,334,336,341,342,348,353, 359,362,364,365,366,367,375,377, 378,381,382,387,390,391,394,396, 398,399,410,411,412,414,415,416, 418,424,425,426,429,430,431,441, 443,451,452,455,456,457,459,464, 470,474,475,478,479,481,484,488, 492,494,498,504,506,507,510,513.
Dog	HFPPV	42	35,249,488,609,610,619,620,625, 626,633 648,656,657,658,663,667, 670,671,672,673,679,681,684,685, 687,688,689,690,697,699,703,704, 706,708,709,710,711,712,716,729, 730,741.
Dog	EOV	6	603,685,763,768,769,773
Rabbit	HFJV	2	185,208
Rabbit	HFOV	8	335,350,358,402,419,445,508,514
Rabbit	HFPPV	10	620,645,647,649,655,664,665,694, 714,716
Cat	HFJV	10	64,126,138,139,160,162,195,196, 269,270
Cat	HFOV	4	311,352,422,450
Cat	HFPPV	5	652,691,692,693 727
Cat	EOV	2	761,770
Sheep	HFJV	1	96
Sheep	HFOV	5	321,389,423,449,483,
Monkey	HFOV	3	316,348,503
Rat	HFPPV	2	602,603
Rat	HFJV	1	115
Rat	HFOV	2	372,373
Rat	EOV	2	765,772
Pig	HFJV	2	164,281
Pig	HFOV	1	494
Horse	HFJV	2	76,115
Goose	HFOV	1	447
Duck	HFOV	1	374
Chicken	HFOV	1	312

TABLE 4: Pathologic lung models

Model	Species	Number	References
OAPE	Dog	20	23,190,231,317,329,348,381,382, 424,427,431,468,488,492,498, 412,656,697,709
OAPE	Rabbit	3	402,514,649
Saline lavage	Rabbit	5	208,335,371,402,445
Saline lavage	Dog	4	133,310,687,688
Saline lavage	Cat	1	126
Immature lungs	Monkey	5	316,348,502,602,603
Immature lungs	Lamb	3	36,442,483
Open chest	Dog	6	119,330,451,685,690,706
Open chest	Cat	1	311
Bronchospasm	Dog	7	33,364,391,464,475,511,699
Air embolism	Dog	2	679,684
Air embolism	Sheep	1	389
Meconium aspiration	Cat	2	160,162
Meconium aspiration	Rabbit	1	694
Bronchopleural fistula	Dog	2	685,741
Tracheal fistula	Dog	2	57,152
Hydrochloric acid aspiration	Dog	2	5,501
Hydrochloric acid plus OAPE	Dog	2	55,58
Bronchopleural fistula plus OAPE	Dog	2	425,697
Hemorrhagic shock	Dog	1	68
Neurogenic pulmonary edema	Dog	1	667
Aloxan pulm. edema	Dog	1	626
Open chest plus OAPE	Dog	1	330

III. - Findings on pathologic lung models:

a). OAPE: Although some authors have claimed that HFV has several advantages over conventional ventilation in OAPE (329,402,425), others concluded that there was no clear difference (231,498,656). However, there are many reports with findings indicating that IPPV (or PEEP) is better than HFV in OAPE: in some of the experiments HFV induced lower PaO_2 (231,381,656,), higher $PaCO_2$ (330,381,498), higher shunt ($\dot{Q}s/\dot{Q}t$; Refs.330,381,382), higher $\overline{PAP}$ (330,381,431), higher PWP (330,498), lower cardiac output ($\dot{Q}$; Refs.23,231,330,709), higher $\overline{P}aw$ (186,231,402) higher Pawp (186,348,431) or higher lung water content (424). Most experiments were done without matching for $\overline{P}aw$, and this might have influenced the results (498).

b). Saline-lavaged lungs: There is less experience with this model, which induces an unstable lung of low compliance (829). The data available seem to indicate that HFV can achieve better gas exchange than PEEP (335,371,402,687). However, there are some reports with unfavourable data on gas exchange (310,371,688) or cardiovascular function (310,687,703,704).

c). Open-chest animals: Although a report claims some advantages of HFV over PEEP in this model (685), and another some disadvantages (119), most studies suggest that there is no difference (330,451,690,706).

d). Bronchoconstriction or mechanical airway obstruction: The data available on this model are not conclusive. Some studies failed to use IPPV controls (33,364,464), one claimed some advantages (699), one no difference (511) and two worse ventilation (391,475). There is only one report of EOV in dogs with obstructed airways (763) and it suggests that EOV can help in ventilation of this model.

e). Other models: The rather limited amount of data on other abnormal lung models suggests that HFV may have some advantages over IPPV in the presence of airway fistulas (685,697,741) and in immature lungs (423,469), but worse in meconium-aspiration models (199,694). In the presence of air embolization, HFV has been found to be equal (389,684) or better (679) than PEEP.

f). Pathologic lung model data grouped according to ventilatory mode: There are very few studies comparing two different HFV modes on abnormal lungs. Available data suggest: HFJV can maintain better gas exchange than HFOV in OAPE in dogs (381,382); HFOV induces a lower $\dot{Q}s/\dot{Q}t$ than HFPPV in dogs with OAPE (488); HFOV induces more liver damage than HFJV in OAPE dogs (348) and than HFPPV in premature monkeys (318). No satisfactory conclusions about differences in HFV types can be drawn from the remaining abnormal lung experiments because there are not enough studies of individual models to be compared.

IV. Overall in vivo research:

The effects of the different types of HFV on many aspects of cardiopulmonary physiology have been studied, but for the sake of clarity only relevant information will be discussed. As data on HFV types other than HFJV, HFPPV and HFOV are scarce, they will be grouped and discussed separately at the end. The majority of the studies compared HFV with IPPV or PEEP; comparisons were seldom made with spontaneous breathing.

a). Lung mechanics

(1) PRESSURE:

It has to be remembered that airway pressure measurements during

HFV are technically difficult and the data reported in many publications are of doubtful value (see under "Measuring Paw during HFV"); this is especially relevant for Pawp.

*$\overline{\mathrm{P}}$aw: It has been claimed repeatedly that one of the major advantages of HFV is to achieve gas exchange with $\overline{\mathrm{P}}$aw lower than IPPV levels, and there are many data to support this view in the three major types of HFV (247,480,570). However, there are also many reports on elevated $\overline{\mathrm{P}}$aw, some with values significantly higher than IPPV levels during HFJV (65,160,190,231), HFOV (402,309,310) and HFPPV (685,703, 704); in others the increases were not statistically significant during HFJV (48,58), HFOV (418,429,430,431,449,450,507) or HFPPV (620,652,667). There is not a clear-cut explanation for these differences, which are probably due to a combination of phenomena. Several factors that affect $\overline{\mathrm{P}}$aw have been identified, they include: location of the tip of the measuring catheter (221,690), amount of entrainment (225,514,), I/E ratio (30,693), Raw (160,464), respiratory system compliance (609,610) injector size (55,610), tidal volume (58,514,610), frequency (30,474, 514), low-pass filter characteristics (369,479), bias flow (362,514), driving pressure (55,58) airway pressure gradients (330,488) etc. It is not clear which of these factors are responsible for the reported differences in $\overline{\mathrm{P}}$aw findings between studies. As $\overline{\mathrm{P}}$aw influences the cardiovascular status (831,841) and FRC (92,498), it is a very important parameter to control, especially when comparisons with IPPV are attempted. Unfortunately, not all the reports include $\overline{\mathrm{P}}$aw measurements (361). The disparity in the hemodynamic effects of HFV reported by different groups seems likely to be due, at least in part, to different $\overline{\mathrm{P}}$aw levels. It can be concluded that even though HFOV usually

induces low $\overline{P}$aw, this is not always the case because several factors can increase $\overline{P}$aw during HFOV.

*Pawp: It has also been claimed that HFV induces lower Pawp than IPPV, thus decreasing the risk of barotrauma (104), an there are several reports with low Pawp during HFV (199,633,652). However, as for $\overline{P}$aw, there are also several publications with Pawp values higher during HFV than during IPPV (60,430,620,690). The factors that influence Pawp are similar to those already mentioned for Paw, and it is also unclear which of them are responsible for the discrepancies. Moreover, for Pawp, frequency response of the measuring system is critical because peak values usually have high frequency components (819) especially during HFJV and HFPPV. This may be responsible for the low values found in several studies using narrow tubings for Pawp measurment, like National Catheter-type multilumen ETT (199,248,249), because their frequency response is quite low (328). Also, some studies suggest that peak pressures at the alveolar level during HFV could be higher than Pawp (314,355), and thus the allegation that HFV has less risk of barotrauma than IPPV may not be as straightforward as it has been claimed.

*Airway pressure gradients and Palv: There is a considerable amount of data, both direct and indirect, to suggest that during HFV $\overline{P}$aw increases as the airway diameter decreases, and is maximal at the alveolar level. Several authors have reported that when the endotube is clamped during HFV, $\overline{P}$aw increases immediately, reaching a value (Poc) which they claim equals $\overline{P}$alv (330,476,645). It is quite possible however, that Poc underestimates the value of $\overline{P}$alv during HFV, because a fraction of $\overline{P}$alv will be lost in raising $\overline{P}$aw towards Poc; also if Poc is higher than $\overline{P}$aw, the compliant small airways will be distended somewhat, further decreasing $\overline{\mathrm{P}}$alv. Indeed, one of the previously-mentioned reports states that in order to induce the same shunt fraction during IPPV and HFV, $\overline{\mathrm{P}}$alv during HFV (assumed to be equal to Poc) had to be 1.5 cm H_2O higher than $\overline{\mathrm{P}}$aw during IPPV (330), thus suggesting that Poc was underestimating $\overline{\mathrm{P}}$alv by around 1.5 cm H_2O. There are two reports suggesting that during HFV lung volume is higher than during IPPV, at the same proximal $\overline{\mathrm{P}}$aw (402,460). Several groups have measuredPaw in small airways and found higher distal $\overline{\mathrm{P}}$aw values (330,348,441,488) which have been confirmed by measurements with a retrograde catheter (330,460). There is no clear explanation for the existence of this pressure gradient during HFOV. One of the factors involved could be a Bernoulli phenomenon, induced by the decrease in gas velocity that takes place when total crossectional area increases in small airways; this induces a decrease in kinetic energy that has to be compensated for by an increase in potential energy (measured as $\overline{\mathrm{P}}$aw) in order to keep energy levels constant (330). Theoretical calculation of the pressure gradients are difficult and involve several assumptions; calculated values suggest that the Bernoulli phenomenon is only partly responsible for the observed pressure gradients (330). It has been postulated that the pressure gradient may also be due to air trapping induced by high respiratory rates (563), or to other unknown factors (364) which might include energy losses due to friction or inertance.

*Esophageal (Peso) and pleural (Ppl) pressures: Although much emphasis has been put on the study of the cardiovascular function during HFV, very little is known about Ppl which is one of the major determinants of $\dot{Q}$; Peso, as an approximation of Ppl, also has not been well investigated. Of the 9 animal studies mentioning Ppl, 4 found that it did not change during HFV (5,164,681,693), 3 that increased (321,449, 703), only in 1 significantly (703) and 2 that decreased but not significantly (671,689). There are 9 reports on Peso, on 3 of them it increased but not significantly (60,389,498) on one decreased significantly (163) and on the remaining 5 no comparison was made with IPPV values (65,457,497,504,727). These data indicate that, in some cases, intrathoracic pressure can be elevated during HFV, and this is probably related to the previously-mentioned air-trapping effect.

(2) VOLUME:

*Lung volume: Although there are very few groups that have measured $\overline{V}_L$ during HFV, it is well established that it is increased above IPPV levels by the three major HFV modes, HFJV (57,60), HFPPV (710,724) and HFOV (457,474). Most of the data have been obtained by monitoring FRC changes induced by HFV rather than by measuring actual $\overline{V}_L$. Obviously, the two major determinants of $\overline{V}_L$ are $\overline{P}$alv, compliance of the respiratory system (Cst), and the factors that affect them (which are discussed in the corresponding paragraphs) will also determine $\overline{V}_L$. It is important to remember that, during HFV, $\overline{P}$aw probably underestimates $\overline{P}$alv and consequently is not as dependable an index of $\overline{V}_L$ as it is during IPPV. Unfortunately, most studies attempting to match $\overline{V}_L$ during IPPV and HFV have used $\overline{P}$aw as an indicator, thus probably ventilating the animals at higher $\overline{P}$alv and $\overline{V}_L$ during HFV. Available indirect data suggest that Cst does not change during HFV (see later), and thus it is not responsible for the increased FRC. A likely cause for the HFV-induced increase in $\overline{V}_L$ is the previously-mentioned increased $\overline{P}$alv, and air trapping caused by high respiratory rates (225,330,563), or else that HFV puts the lung close to the deflation limb of the pressure/

volume (P/V) curve (402).

*Compliance: There are no direct measurements of Cst of the respiratory system during HFV, which is perhaps due to the difficulties involved in measuring FRC and $\bar{P}$alv. There are very few reports on the changes in P/V characteristics of the respiratory system induced by HFV (that is, comparing P/V before and after HFV), and their conclusions differ. Two studies found slight non-significant decreases in Cst, one of them only at low volumes (503) and the other attributed the changes to increased muscular tone (366). In a third report, the data suggest a non-significant increase in Cst (452), and in another study no change was observed (652). In saline-lavaged rabbit lungs HFOV maintained higher Cst than PEEP (445). None of these studies used actual lung volumes to position the P/V curves. Of the several factors that may affect the P/V characteristics of the respiratory system, vibration could increase respiratory muscle tone (823), but probably does not change surfactant activity (see later); the effects of HFV on lung blood volume have not been reported.

(3) SURFACTANT:

There are few studies on the effect of HFV on surfactant, and most of them suggest there is no change from IPPV (302,359,483,503). Only one, a more elaborate study, suggested an increased surfactant turnover in rabbits (419).

(4) COLLATERAL VENTILATION ($\dot{V}$coll) AND AIRWAY RESISTANCE:

There are no studies of $\dot{V}$coll during HFV, although several reports have discussed its importance (323,406,494,552,561). There are also no measurements of Raw, but the diameter of the airways (28,209,364) and large-airway muscle tone (33) have been found to increase during HFV.

b). Gas exchange, oxygen transport and ventilation

•PaO_2 Together with $PaCO_2$, PaO_2 is one of the most common parameters mentioned in the HFV literature. Although the majority of the reports show normal or high PaO_2 values, there are many cases of PaO_2 lower than IPPV (or PEEP) levels (Table 5). Many factors have been reported to modify PaO_2 during HFV, the most important being $\overline{V}_L$ (181), $\overline{P}aw$ (498,654) and $\dot{V}min$ (140,345,612,647); other parameters thought to play a role in oxygenation include I/E ratio (30,568), insuflation catheter position (108,690), PEEP (160), insuflation catheter size (610), bias flow (514), etc. In the previously-mentioned reports of relative hypoxemia, low PaO_2 was mainly due to circuits or respiratory parameters unable to maintain adequate alveolar ventilation. It should be emphasized that in many studies HFV was compared with IPPV without matching for $\overline{P}aw$ (361). In the cases where $\overline{P}aw$ was the same, it is possible that $\overline{P}alv$ was higher during HFV (see under "Airway pressure gradients and Palv") which may have been the cause for increased PaO_2. It can be concluded that even though HFV can maintain adequate PaO_2 levels, several physiological and technical factors that can induce a drop in PaO_2 during HFV have been reported.

• Alveolar PO_2 (P_AO_2), oxygen gradients in the airway and alveolo-arterial O_2 pressure difference ($P[A-a]O_2$): It has been suggested that during HFV there is a continuous PO_2 gradient from the airway opening to the alveolus (439,474). However the frequency response of the catheter-detector systems available might not be fast enough to detect the fluctuations in PO_2 caused by bulk movement of gas, that would be anticipated in zones II and III of Slutsky et al. (572).

TABLE 5: Literature findings for PaO_2, $P(A-a)O_2$, and $PaCO_2$ data. For details see text.

Findings	Number	References
Higher PaO_2 (*)	9	11,191,371,402,504,664,665,685,704
Higher PaO_2 (NS)	21	57,90,160,181,209,210,281,372,381,418, 452,488 503,626,647 652,671,688,689,690,
	697	
Lower PaO_2 (*)	7	58,231,331,336,381,475,504
Lower PaO_2 (NS)	15	5,150,160,260,371,391,481,494,498,613, 656,671,681,687 711
Similar PaO_2	25	48,60,108,163,190,199,209,223,256,308, 382 389,402,429,430,431,460,633,657,663, 673,686,693,709,716
PaO_2 not compared	35	10,23,30 87,115 126,133,140,155,157 164, 244,245,249,261,277,315,323,342,410,422, 423,450,457,474,492,514,609,610,625 691' 699,708,727,741
Higher $P(A-a)O_2$ (*)	3	316,634,694
Higher $P(A-a)O_2$ (NS)	7	108,160,162,209,442,460,633
Lower $P(A-a)O_2$ (*)	6	160,191,208,310,372,373
Lower $P(A-a)O_2$ (NS)	1	626
Similar $P(A-a)O_2$	5	185,190,498,504,613
$P(A-a)O_2$ not compared	5	126,457,474,514,708
Higher $PaCO_2$ (*)	9	58,108,181,260,330,336,381,460,494
Higher $PaCO_2$ (NS)	21	60,119.160,162,244,310,345,372,374.382 399,429,481,489,498,506,652,656,681,686, 697
Lower $PaCO_2$ (*)	10	11,205,209,373,450,503,504,664,685,704
Lower $PaCO_2$ (NS)	12	57,190,199,210,371,391,418,430,665,687, 688,741
Similar $PaCO_2$	19	8,28,48,163,270,308,402,431,494,604,613, 633,657,658,663,670,686 693,709
$PaCO_2$ not compared	54	5,10,30,33,58,66,67,68,108,115,126,133, 138,139.140,155,164,181,223,245,249.261, 277,281,313,323,342,352,362,390,410,422, 423,425,441,457,464,474,497,514,609,610, 619,625,645,667,673,790,791,794,708,711, 712,727

*, differences statistically significant.
NS, differences not statistically significant.

It is possible that similar "continuous" gas-concentration gradients could be encountered during IPPV if a slow-enough measuring system was used. There is only one report of P_AO_2 values, which were calculated in men during HFPPV (606). There are many publications with $P(A-a)O_2$ data (Table 5), with a scatter of findings as it would be expected from the PaO_2 findings reported previously. No other conclusions can be drawn from $P(A-a)O_2$ data. It has to be pointed out that as $PaCO_2$ can be quite low during optimal conditions of HFV, high $P(A-a)O_2$ values could be associated with normal PaO_2 levels.

* O_2 delivery (O_2Del), O_2 consumption ($\dot{V}O_2$), mixed venous PO_2, ($P\bar{v}O_2$) and arterio-venous O_2-content difference ($C[a-\bar{v}]O_2$): There are very few data available on these parameters. Reported O_2Del values are either normal (262,613) or high (significantly: Refs.601,633; nonsignificantly: Ref.697), as it could be expected when most authors claim that HFV induces normal or high PaO_2 and cardiac output ($\dot{Q}$). However there is a report of a significant decrease in O_2Del (703); in other publications comparisons with IPPV levels were not made (245,488,609). Reported $\dot{V}O_2$ also tends to be high (457,494,504,633), and it has been suggested that a rise in tissue metabolism induced by HFV may be responsible for the increase (457). There is scatter of the few $P\bar{v}O_2$ data available and no conclusions can be drawn: there are reports of a nonsignificant increase (281,430), decrease (119), no change (418,663), and there is a report without comparison with IPPV (245). The only two comparisons available of $C(a-\bar{v})O_2$ between HFV and IPPV showed no change (235,633).

* $PaCO_2$: In order to prove that a ventilatory mode works, it must maintain normal or low $PaCO_2$ values, and many reports have shown that

HFV is effective in achieving this (Table 5); however, in some studies, $PaCO_2$ levels were higher during HFV than during IPPV. Several factors that determine $PaCO_2$ have been studied during HFV, the most important being the ones that determine alveolar ventilation, mainly tidal volume (249,457,478) and rate (244,479,690), and related parameters like gas entrainment volume (55,625), injector-catheter size (58,610) and position (108,690), driving pressure (55,249), I/E ratio (30,609), bias flow (362,457), etc. Dead space to tidal volume ratios (V_D/V_T) have been measured during HFV (see later) but the values were not compared to $PaCO_2$ levels. An increase in V_D/V_T may be responsible for the increase in $PaCO_2$ at high $\overline{V}_L$, observed in some studies (181,219), but these findings are controversial (369,479). Early HFV studies suggested that there was an optimal frequency for CO_2 elimination (323,430,514), but this was later attributed to a circuit artifact (338) and was not confirmed in other studies (249,402,441). However there are reports which suggest a true optimal frequency (314,457,625,712), that could be related to the resonant frequency of the respiratory system (395,409, 818). In any case, there seems to be of little advantage in ventilating at rates faster than 200 bpm during HFJV (11,68,173,219) and HFPPV (625,712). During HFOV there is usually not much improvement at rates above 30 Hz, unless large V_T are used (312,457). It can be concluded that even though HFV can usually induce hypocapnia, unless the ventialtory parameters are optimized, CO_2 accumulation can ensue.

* Alveolar PCO_2 (P_ACO_2) and CO_2 gradients in the airways: An estimate of P_ACO_2 can be obtained from an end-expiratory gas sample after stopping HFV, a technique that has been used in a few experiments (457,464,478,625). There is only one publication that reports P_ACO_2

values (625), and they followed $PaCO_2$ closely as frequency increased. There are several reports of gradients in CO_2 concentration down the airway (210,474,484,491,512); but as mentioned before for O_2, a fast-enough sampling system might have detected fluctuations in CO_2 concentration with each V_T, at least in the first few airway generations (175).

* V_D/V_T, V_{Dphys} and V_{Dana}: The classical concepts of dead space ventilation do not apply to HFV, as it is theoretically impossible to ventilate with $V_T < V_{Dana}$. But there are other factors that make it difficult to understand the meaning of "dead space" during HFV: the mixing effect of the airway bifurcations implies that the interaction of flow with the airways could be as important as the total volume of the airways (V_{Dana}); the interregional gas transport and difference betwen inspiratory and expiratory flow profiles indicate that the volume of gas left in the lungs at "end expiration" during HFV has little to do with V_{Dana}. Rebreathing has also a completely different meaning for the reasons mentioned in the last sentence, but also because air entrainment during HFJV and a large portion of expired gas during HFOV constitute a significant fraction of V_T; the enhancement of gas diffusion induced by HFV tends to overcome the physical barrier of V_{Dana}. Using Bohr's equation (812), V_D/V_T during HFV has been calculated by some authors assuming that there is no CO_2 in the inspired air filling V_D (460,504, 613,647). But this is probably incorrect due to the interregional gas transport, rebreathing, CO_2 gradient in the airways, mixing due to airway bifurcations, etc. This assumption produces an underestimation of V_D, and the calculated values of V_D/V_T during HFV probably do not have physiological meaning.

* Shunt: There are many studies with $\dot{Q}s/\dot{Q}t$ data but no clear trend can be observed on the effects of HFV (Table 6). Also, no clear correlation could be observed between the changes and possible etiologic factors, like PAP or $\overline{P}aw$. The available $\dot{Q}s/\dot{Q}t$ data are thus inconclusive. Several studies were done using the multiple gas technique to calculate the shunt fraction (849) which might be subjected to artifacts during HFV (430), and the others with standard formulas using O_2 content (852). To apply this latter method, the inspired concentration of O_2 has to be measured intratracheally (439) and then used to calculate P_AO_2 with the standard alveolar air equation (360).

* Ventilation/perfusion ratio ($\dot{V}/\dot{Q}$): There are several studies of $\dot{V}/\dot{Q}$ distribution during HFV that used the multiple-gas technique, and all of them found an increase of ventilation to high $\dot{V}/\dot{Q}$ areas (430,447, 460,709). Subsequently this has been found to be an artifact of the method probably due to enhanced dilution of high solubility gases (like acetone) into the airway lining fluid (430). Two studies using intravenous radioactive ^{133}Xe to assess $\dot{V}/\dot{Q}$ concluded that HFV improves $\dot{V}/\dot{Q}$ matching at moderate frequencies and small V_T, but not at high rates and high V_T (331,337). The only report of $\dot{V}/\dot{Q}$ ratios using combined intravenous and inhaled gas (Krypton) suggested that HFV improves $\dot{V}/\dot{Q}$ matching by decreasing ventilation to the normally relatively overventilated upper lung regions (384).

4

c). Hemodynamics

* Heart rate (HR): There are many data on the HR response to HFV but there does not seem to be a consistent trend (Table 6). Several factors could be responsible for the scatter of data, but in most

TABLE 6: Literature findings for $\dot{Q}s/\dot{Q}t$, HR, SAP and SVR.

Finding	Number	References
Higher $\dot{Q}s/\dot{Q}t$ (*)	4	58,381,391,671
Higher $\dot{Q}s/\dot{Q}t$ (NS)	8	330,382,424,475,481,501,613,656
Lower $\dot{Q}s/\dot{Q}t$ (*)	4	160,494,703,704
Lower $\dot{Q}s/\dot{Q}t$ (NS)	4	308,329,460,671
Similar $\dot{Q}s/\dot{Q}t$	5	11,162,511,633,709
$\dot{Q}s/\dot{Q}t$ not compared	6	10,23,245,425,488,670
Higher HR (*)	1	693
Higher HR (NS)	3	160,450,452
Lower HR (NS)	6	119,244,330,381,410,685
Similar HR	19	48,108,164,260,262,269,308,336,352, 431,456,503,613,633,657,658,663,667, 681
HR not compared	8	133,245,504,609,610,691,729,741
Higher SAP (*)	2	163,185
Higher SAP (NS)	12	5,119,160,199,381,450,452,494,498, 671,679,687
Lower SAP (*)	2	58,703
Lower SAP (NS)	7	48,57,164,402,504,602,685
Similar SAP	25	96,108,210,255,260,262,269,270,313, 316,330,336,352,382,479,503,613,623, 657,658,663,667,673,681,716
SAP not compared	10	23,133,140,244,245,514,609,619,647, 691
Higher SVR (*)	1	255
Higher SVR (NS)	2	160,685
Lower SVR (NS)	3	381,633,685
Similar SVR	2	382,613
SVR not compared	3	244,245,609

Symbols as in Table 5. For details see text.

publications there is not enough information to determine their exact role. Some of these factors are: changes in the level of anesthesia, pharmacological action of the anesthetics or neuromuscular blocking agents (especially when given as a bolus), changes in sympathetic or vagal tone related to HFV, hyper- and hypothermia etc. The role of other factors, like the changes in blood gases and acid-base status can be determined from available data. Very few reports have dealt with the role of cardiovascular reflexes during HFV but the available data suggest that these responses are similar to those occurring with IPPV (453,456).

* Systemic arterial pressure (SAP) and systemic vascular resistances (SVR): Most HFV studies report SAP, and although most have found no change, in some reports both hyper- and hypotension have been observed (Table 6). In 8 of the 14 reports with high SAP, a concommitant rise in $PaCO_2$ or cardiac output $\dot{Q}$ was also observed (5,119,160,163,381,494,498,671), which might have been responsible for the rise in SAP. Opposite changes were observed in all 9 reports with low SAP except in one (402). There are few reports with SVR values and no clear trend can be defined (Table 6). In all cases of reported variations in SVR, changes in $\dot{Q}$ or $PaCO_2$ could be identified as the probable responsible factors. It can be concluded that HFV per se does not change SAP or SVR.

* Pulmonary artery pressure (PAP) and pulmonary vascular resistances (PVR): There is enough evidence in the literature to suggest that HFV does not decrease PAP: it either increases or does not change (Table 7). Available data on PVR during HFV indicates a tendency for higher values than during IPPV (Table 7). In all but 3 (5,255,452) of the reports of increased PAP or PVR, one or several of the following potential factors (811) could be identified: decreased PaO_2 or increased $PaCO_2$, FRC or $\overline{P}aw$. These findings suggest that HFV per se does not induce pulmonary hypertension unless there is a concomitant change in blood gases or lung volume.

* Pulmonary artery wedged pressure (PWP): There are few reports with PWP data, and the trend is for an increase or no change over IPPV levels (Table 7). Of the 6 publications in which PWP was increased, a high $\overline{P}aw$ was also present in 3 (58,685,703), suggesting that a zone I-II of West creating a vascular-waterfall effect (850) could be involved in the rise in PWP.

* Left-ventricular end-diastolic pressure (LVEDP) and left-atrial pressure (LAP): There are only two reports of LVEDP during HFV (663,673) and one of LAP (321) and all concluded that HFV did not induce significant changes in these parameters.

* Central venous pressure (CVP): Few experiments report CVP values and there is a scatter of results which obscures the understanding of the effects of HFV (Table 7). Only in 2 of the publications (119,689) could the variation in CVP (lower) be related to a decrease in $\overline{P}aw$.

* Cardiac output ($\dot{Q}$): There are many studies with data on $\dot{Q}$ during HFV, and even though it has been suggested that $\dot{Q}$ does not change or it is increased, there are many publications showing decreased $\dot{Q}$ values

TABLE 7: Literature findings for PAP, PVR, CVP, and $\dot{Q}$

Finding	Number	References
Higher PAP (*)	7	160,162,330,381,494,685,703
Higher PAP (NS)	10	5,58,119,281,321,430,431,449,450,452
Lower PAP (*)	1	96
Lower PAP (NS)	1	687
Similar PAP	14	160,199,210,262,336,389,498,504,613, 657,658,663,673,681
PAP not compared	9	66,140,244,245,264,430,609,610,619
Higher PVR (*)	4	160,162,255,381
Higher PVR (NS)	1	119
Lower PVR (NS)	2	199,685
Similar PVR	1	382
PVR not compared	4	23,66,244,245
Higher PWP (*)	1	703
Higher PWP (NS)	5	58,330,452,498,685
Similar PWP	6	119,199,262,389,494,681
PWP not compared	5	23.244,245,424,619
Higher CVP (*)	2	693,703
Higher CVP (NS)	7	185,199,269,270,452,673,681
Lower CVP (NS)	5	71,119,164,685,689
Similar CVP	3	262,450,613
CVP not compared	8	23,140,244,245,609,610,619,691
Higher $\dot{Q}$ (*)	5	65,163,199,336,633
Higher $\dot{Q}$ (NS)	9	231,381,481,494,498,656,671,686,697
Lower $\dot{Q}$ (*)	7	58,96,231,251,330,703,704
Lower $\dot{Q}$ (NS)	23	11,23,48,60,119,160,164,244,281,321, 430 442,449,450,452,494,504,658,681, 685,687,708,709
Similar $\dot{Q}$	19	5,140,162,191,210,262,323,382,389,431, 457,475,511,613,657,663,667,673,690
$\dot{Q}$ not compared	6	124,126,245,415,609,702

Symbols as in Table 5. For details see text.

during HFV (Table 7). The following factors could be responsible for low $\dot{Q}$ values: increased afterload, decreased preload, increased intrapulmonary pressures or $\overline{V}_L$, hypoxia and hypocapnia. There were only 3 of the 30 publications with decreased $\dot{Q}$ values (96,658,709) in which none of the previously-mentioned factors was present. When the reverse factors (except increased PaO_2) were considered in the 14 reports with high $\dot{Q}$, there was only one (65) in which none of the factors was present. The parameter most frequently associated with low $\dot{Q}$ was increased $\overline{P}aw$, and hypercapnia with high $\dot{Q}$. From this it can be concluded that HFV can change $\dot{Q}$ only through secondary physiologic changes.

* Left-ventricular stroke work (LVSW) and right-ventricular stroke work (RVSW): There are only 4 reports of RVSW during HFV: in one no change was induced over IPPV levels (382), in another it increased (381), in the third no comparison was made (66) and in the fourth it decreased (703). The reports on LVSW are also contradictory: two found increased values, associated with a rise in SAP (119) or in $\dot{Q}$ (65), in one it was decreased without apparent reason (381), in one it was decreased together with SAP (703), in another there was no change (382), and in two no valid comparisons with IPPV were made (245,685).

d). Lung defense mechanisms

* Mucociliary function (MCF): There are very few data on MCF during HFV, only one full paper and 3 abstracts have been published. Two abstracts reported that HFV did not have a significant effect on tracheal transport rates (151,307). The paper confirmed unchanged tracheal transport rates after HFOV or IPPV (however no control

measurements were made during IPPV), but concluded that HFV almost completely abolished the clearance of sulfur colloid particles, due perhaps to changes in mucus production and flow (429). And finally there is an abstract reporting an increase in cilia beat frequency during HFV in vitro (358).

* Airway secretions: There have been 14 reports of increased amounts of airway secretions induced by HFV, most of them in humans (see later) and only two in animals (195,429). Although some authors have postulated that this represents an improved clearance of secretions, it could also be due to an enhancement in the production of secretions induced by HFV (429), which could create a risk of airway plugging.

e). Miscellaneous

* Organ blood flow: There is one report suggesting that HFV does not significantly affect regional blood flow (brain, myocardium, skin, muscle, liver, adrenals, jejunum, pancreas and kidney), as assessed by a radioactive microsphere technique (673). Another report also suggests that HFV does not significantly change cerebral, pulmonary, cardiac or renal blood flows, as compared to IPPV (619).

* Lung water and lymph flow: There are few and contradictory data on the effects of HFV on lung water. A species difference may be involved because two studies with normal lambs found no change (321, 449), and in studies with dogs, either normal (451) or with oleic-acid induced pulmonary edema (424,704), lung water was elevated by HFV. The results of lung lymph flow studies are also contradictory: decreased flow was found in normal lambs (321) and in lambs with elevated left atrial pressure (449); in sheep with air embolism, lymph flow was

similar to IPPV levels (389); in normal dogs lung lymph flow was increased by HFV (451). More data are needed to understand the role of HFV on lung fluid balance.

* Intracranial pressure (ICP): There are 6 reports comparing HFV and IPPV in which no change in ICP was observed (270,450,663,667,673, 723). Only two communications found increased values (5,269) but the cause remained obscure. All the authors agree in that the respiratory fluctuations in ICP (or brain surface movement) are diminished or abolished by HFV.

* Renal function: Other than the previously-mentioned organ-flow studies, there are very few data on renal function during HFV. An incomplete report in two dogs indicated small differences in urine volume and osmolality, as compared to IPPV (690); another study which compared HFV to IPPV found similar renal responses to left atrial receptor stimulation (456). No changes in renal function parameters have been observed during 24 hr of HFV (245,316); minor impairment in several parameters (glomerular filtration, renin levels, sodium excretion and urine volume) has been reported when HFV was compared to spontaneous breathing with added continuous positive airway pressure (164). These observations are insufficient to draw any conclusion on renal function during HFV.

* Core temperature: During HFV (especially HFJV and HFPPV), a large volume of gas at room temperature reaches the airway cooling it (unless a warning system is used), and the ventilator's humidifier circuit may further decrease the gas temperature through evaporative heat loss (64). It has been postulated that the cooling effect of HFV may be considerable and overcome the body's thermoregulatory mechanisms,

causing hypothermia (64). Indeed, there are several reports in the literature of decreased core temperature during to HFV (7,245,336,681).

* Long-term effects: Although HFV has been used in humans for extended periods of time (up to a maximum of 75 days, Ref.168), most animal studies have lasted only a few hours. There are only 4 reports of HFV experiments lasting more than 24 h. Rehder *et al.* found no changes in lung mechanics (but some structural damage) in dogs after 36 h of HFOV (452). Doyle *et al.* monitored the effects of humidification on the tracheal mucosa of dogs after 72 h of HFJV and found "no significant differences between the humidified groups" in the tracheal mucosa, but there was no comparison with IPPV and no other effects were monitored; two "premature deaths" were attributed "to sepsis" (78). Frey *et al.* studied a group of "normal" dogs for up to 4 days of HFJV and found less pathological changes and better survival than when the animals were ventilated with IPPV (90), however the short survival of the IPPV animals (average 2.35 days) suggests that the experimental conditions might not have been optimal. DeLemos *et al.* ventilated a group of premature baboons for 4 days with PEEP, HFOV and HFPPV, and found better oxygenation at lower $\overline{P}$aw during HFV, although the animals ventilated with HFOV showed some histological changes in the liver and lungs (348); no deaths were reported.

* Pathologic findings: Although some studies suggest that HFV does not induce pathologic changes (78,217,654), other reports indicate the opposite. The following histolgic abnormalities could have been related to HFV: white-cell infiltrates in the lung (79,90,136,195), alveolar damage (348,714), airway damage related to humidification (188,195), atelectasis (90,452), liver damage (316,348), lung hemorrhage (90),

interstitial emphysema (343), pulmonary edema (90), and pleural effusion (7). Most of these findings could be considered as anecdotal and lacked adequate controls, however their potential importance cannot be ignored in view of the lack of proper long-term studies. In experiments with abnormal lungs, pathologic findings similar to IPPV have been reported (208,371,469), but some authors have found less lung damage (321,335, 449). Barotrauma and airway damage related to trans-tracheal puncture for HFJV, will be discussed later under "Complications".

Human studies

I - Normal-lung experiments:

There are several studies of HFV on normal volunteers which have been used to study technical or theoretical aspects of HFV. HFV has been also used on patients with "normal" lungs: during laryngoscopy, bronchoscopy, airway or chest surgery, anesthesia, cardiopulmonary resuscitation, and central respiratory insufficiency.

a) Technical and theoretical studies: Normal volunteers have been used to study the following aspects of HFOV: blood gas changes and apnea time (338), factors of CO_2 elimination (369), nitrogen washout (437,486) and xenon washin (357). Four of these studies (357,369,437,486) were done in unintubated subjects.

b) Laryngoscopy: HFJV has been used successfully to ventilate patients during laryngoscopy and microlaryngeal surgery; there are 8 reports of this technique in the literature (6,9,62,69,86,116,132,165). There are also 5 reports of so-called laryngoscopic HFPPV (612,632,637, 719,732), but as mentioned earlier, this technique is almost identical to HFJV. The advantages of HFV during larynoscopy will be discussed later.

c) Bronchoscopy: HFJV has been used also during bronchoscopy (rigid and flexible) with success, and there are 6 reports in the literature of this technique (70,88,89,165,274,719). HFPPV during bronchoscopy has been reported in 9 studies (83,610,612,631,634,637,741, 713,732), but again, it is very similar to HFJV.

d) Airway and chest surgery: HFJV has been successfully used to ventilate patients during major tracheobronchial surgery, even though large air leaks were present during the intervention (21,77,156); HFPPV has also been used, but technically it can be considered equivalent to HFJV (83,628). Two studies suggest that HFV can be effective in maintaining gas exchange in patients during open-chest surgery (81,700).

e) Anesthesia: Besides a number of reports on the use of HFV during intravenous anesthesia (31 studies, see Table 8), volatile anesthetic agents have has been delivered through HFV circuits (6,165, 629,630,701,719).

f) Cardiopulmonary resuscitation: The use of HFJV transtracheally has been claimed as an alternative technique to ventilate patients during cardiopulmonary resuscitation (150).

g) Central respiratory insufficiency: HFV has been used successfully to ventilate a few patients with central respiratory insufficiency (85,279,485).

II. Studies in humans with abnormal lungs

a) Acute respiratory insufficiency (ARI): Although there are many reports on HFV of patients with ARI (a total of 30, see Table 8), the majority lacked proper controls, and were usually done in patients who "did not respond to conventional therapy"; a total of 13 studies were case reports. The majority of the studies concluded that HFV was equivalent to or better than IPPV in the management of ARI patients. Most of the patients had adult respiratory distress syndrome (ARDS), others had chronic obstructive pulmonary disease (COPD) or central respiratory insufficiency, and are discussed separately. Patients with bronchopleural fistulas and neonates, will also be discussed separately. There is only one study which includes a large group of patients with randomization and controls (52), and although there are some design questions (how comparable the groups were, effect of crossover, adjuvant therapy, etc.), it can be accepted as satisfactory. This study included mostly patients with widespread malignancies, 152 of them ventilated with HFJV and 157 with IPPV. It is interesting to note that although some patients who could not be ventilated with IPPV improved with HFJV, the reverse also occurred. The conclusion of the study was that there were no differences in terms of mortality and morbidity between HFJV and IPPV. Further studies with more representative patients and other HFV modes will be needed before satisfactory conclusions can be made on the role of different HFV modes in ARI.

b) COPD: Of the 9 studies that include HFV of patients with COPD, 7 have used HFJV (6,39,43,69,127,214,232), and one each HFOV (338) and HFPPV (640). They all show that HFV can be used in this type of patient, but several reports suggest that it may not be as good as IPPV for CO_2 removal (39,43,232,338).

c) Bronchopleural fistual (BPF): The ventilation of patients with BPF is probably one of the main indications for HFV because satisfactory gas exchange can be maintained inspite of large leaks (367). There are 32 reports of HFV in patients with BPF (Table 8), including both neonates and adults, but they are mostly anecdotal reports including very few patients; there are no randomized control studies available. All the reports, except two (123,258), suggest that HFV was better than IPPV in patients with BPF. Most studies were done with HFJV, there are only 2 using HFOV (319,420) and 4 using HFPPV (713,722,731,742).

d) Infant respiratory distress syndrome (IRDS): There are a total of 16 reports on the use of HFV in neonates with IRDS (Table 8), usually involving few patients and without adequate controls. Most of the studies conclude that HFV was better than IPPV for the management of the patients, especially when there was associated interstitial emphysema (618,654,707,742).

e) Airway secretions: In 10 of the studies involving humans, an increase in airway secretions was noted (4,21,130,214,276,420,606,677, 731,734); in two reports it is stated that this represented a problem for the management of the patients (21,420). Although some authors suggest that the increase in airway secretions is due to an improved clearance, the possibility of an augmented production cannot be ruled out (429). The fact that in several studies the increase in secretions was maintained during the periods of HFV suggests that it was due to an increase in the production of secretions.

ADVANTAGES, INDICATIONS, DISADVANTAGES AND COMPLICATIONS OF HFV

Foreword:

Although HFV was first used some 15 years ago, it took until 1979-1980 before it gained widespread use. Thus the experience available is rather limited, and although several advantages of HFV have been claimed, very few have been demonstrated conclusively; also, the indications are not well established. Similarly, although a few disadvantages and complications have been identified, as experience with HFV increases more problems are to be expected. The "trendiness" in many reports that try to demonstrate how good HFV is, together with the lack of appropriate controls in most studies, makes it more difficult to define the role of HFV in clinical practice.

Advantages and Indications

a) Surgery and Anesthesia: The most frequently claimed advantage of HFV is the management of patients during respiratory or brain surgery (Table 8). The decrease or abolition of respiration-induced movements of the lungs, larynx or brain facilitates the surgery. These surgical procedures could constitute an indication for HFV, but the greatest experience (and it is minimal) is with laryngeal surgery. Besides the lack of laryngeal movement, another advantage during laryngeal surgery is the expanded field of view for the surgeon. There are 4 reports claiming that anesthesia is easier with the use of HFV because lesser amounts of drugs are required (69,269,572,677); but more experience is needed before anesthesia can be considered to be an indication for HFV.

b) Barotrauma: It has been claimed repeatedly that HFV can ventilate with lower $\overline{P}aw$ and Pawp, but s mentioned earlier this is not always the

TABLE 8: Reported uses of HFV in humans, and FCV.

For details see text.

Use	Number	References
Anesthesia	31	6,12,83,86,87,89,97,112,116,118,156,165,180, 182,193,234,248,266,345,628,629,630,676,677, 700,702,722,723,724,732,827
ARI	30	4,19,43,49,52,54,56,71,75,82,92,104,121,123, 131,154,167,168,172,230,232,237,257,338,601, 606,639,640,705,723
BPF	30	13,21,22,26,29,40,43,49,51,75,84,104,121,123, 131,169,170,172,179,182,205,248,257,258,319, 420,713,722,731,742
IRDS	16	29,111,172,205,251,347,421,607,608,614,618, 638,654,695,707,742
Brain surgery	19	6,12,83,86,97,116,119,165,180,182,234,266, 269,274,567,604,628,722,732,
FCV	33	12,71,176,186,190,191,210,249,601,605,607, 608,613,614,615,617,618,620,623,638,639,640, 641,664,665,676 698,708,710,711,712,715,742

case, and it is not clear what happens to Palv. There are 5 reports claiming that HFV reduces barotrauma (31,338,361,371,572), but the available evidence is still inconclusive. However, it seems clearer that HFV may be indicated in the management of patients with BPF or extensive airway disruption. The safety problems involved have not been addressed sufficiently.

c) Miscellaneous: The following have been claimed as advantages of HFV by some authors: better hemodynamic tolerance, safer suctioning, easier wean ing, improved CO_2 clearance, lower inspired O_2 concentration required, better tolerance and less ventilator fighting by patients, faster start of ventilation during CPR. These are mostly anecdotal uncritical claims and there is not enough experience to suggest from them specific indications for HFV.

Disadvantages and complications

The complications reported in this section were encountered during HFV, however in several cases direct causal relationship could not be established.

a) Technical: The fast rates used during HFV require sophisticated ventilators that are more difficult to manage, noisier and more prone to mechanical failure than conventional ventilators. There is a report in the literature of a complication due to mechanical failure, which involved the aspiration of particulate material originating from a damaged valve (44). There is another report of mechanical failure of a ventilator (130), but no complications are mentioned. Kinking of the injection catheter (21,116,169) and disconnection (131) have also been reported. It is likely that more problems have occurred but have not been reported.

b) Barotrauma: With the high minute volumes used in HFV, a life-threatening situation can occur in a few seconds if a valve mechanism develops impeding expiration (for example, during HFOV at 20Hz and V_T of 150 ml, 3 liters of gas are delivered into the airway every second). There are several reports in the literature (all during HFJV) of an acute increase in Paw due to this mechanism (21,116,193,232). Other cases of increase in Paw and possible barotrauma have not been related to a valve mechanism (9,29,54,82,99,108,170,249,335,420,608,713). There is a report of distal airway damage in premature baboons, induced by HFPPV (603).

c) Humidification: It is technically complicated to achieve good humidification of inspired gases during HFV, and there are several reports of airway damage due to insufficient humidification (21,151, 205). Airway plugging with mucus has also been reported (21,64,137,169, 205,420,429 452), perhaps due to inadequate humidification added to the above-mentioned increase in secretions.

d) Trans-tracheal ventilation: The insertion of a catheter through the tracheal wall is an invasive procedure that can induce many complications, including: subcutaneous emphysema (12 34,35,80.95,253, 254,260), hemorrhage (12,224,238,250,253,260), kinking of the catheter (80,238,260,261), cough (253,465), hematoma (253), pneumatocele (34), and air embolism (216).

e) Metabolic acidosis: There are many reports of metabolic acidosis developing during HFV (4,208,315,323,352,359,410,412,422,441,452,474, 492,498,602,654) and some authors have attributed it to a side-effect of the anesthesia (609,690). However, a direct effect of HFV cannot be ruled out. This effect could be explained by an HFV-related disturbance in cellular metabolism (457) or low $\dot{Q}$ (613).

f) Miscellaneous complications: Other less frequent complications encountered during HFV include: hemoptysis (170,257,608) atelectasis (348,452), arrhythmia (260,631), bronchoconstriction (70,266), hypothermia (21), psychological intolerance (4,21,99) and life-threatening abdominal distension (62).

COMPARISON OF DIFFERENT HFV MODES

HFJV, HFPPV and HFOV

There are very few studies comparing different HFV modes, and none of them involved humans. Available data suggest: HFJV may be better than HFOV in removing CO_2 in abnormal lungs (381,382); similar factors are involved in CO_2 removal during HFJV, HFPPV and HFOV (387,625); oxygenation may be better during HFOV than during HFPPV due to higher $\overline{P}$alv (348,488); liver damage is worse during HFOV than HFPPV (316,348); HFPPV may induce more parenchymal damage than HFOV in immature lungs (316).

Technically it might be more difficult to maintain an HFOV machine running in a clinical setting. In terms of indications, HFJV seems to be advantageous in BPF, and is easier to use during laryngeal surgery and endoscopy. Otherwise, there are no data to suggest that any HFV mode is better for use in a clinical setting. For studies on gas exchange mechanisms, HFOV seems to be better because the ventilatory variables are easier to control.

Fast conventional ventilation

In a total of 33 reports HFV was administered with a conventional ventilator adjusted to give fast rates (Table 8). Most studies suggest that high rates have some advantages (mainly better gas exchange and lower $\overline{Paw}$) over conventional IPPV rates, especially in diseased lungs. Only one study (613) maintains that a special ventilator with very low compressible volume is to be used and performs better than a fast conventional respirator. However in this study the methods used to measure Paw and flow might have induced some errors in the measurements.

Superimposed HFV

Data on superimposition of HFV on IPPV are scarce, and although this technique may improve gas exchange (124,191,251,257,372,373,427, 504,704,731) the hemodynamic effects and the possibility of barotrauma have not been explored sufficiently to recommend its use.

External oscillatory ventilation

EOV has been shown to be effective in ventilating both animals (770,773) and humans (762,766) . The chamber mode has not been developed for use with humans; the cuff system tends to decrease FRC (773) which may be deleterious in clinical practice. It has been claimed that HFV improves mucus clearance (768), but the possibility of increased mucus production has not been ruled out. The deleterious effects of vibration in the body (769) could also occur during EOV, but they have not been studied in detail. It seems that EOV is as effective as HFOV, at least in small animals (765).

THE HFV LITERATURE

Methodology used for this review

Material for this review was obtained from the following sources: systematic review of indexes of journals involved in cardiorespiratory research; systematic review of references cited in HFV papers; on-line computer search (Medline). All the articles encountered were loaded in to a desk-top computer (IBM Personal Computer) using data storage retrieval software (Scimate Corp.). The data entered for each article were: HFV type(s); file number; journal; volume, page, year; abstract, editorial, letter or full article; title; principal authors; laboratory and/or city; topics covered; other articles with the same data. The following items were abbreviated: journal, title, laboratory and topics. Arranging the articles by authors and laboratories uncovered material published more than once; arrangement by journals gave knowledge of which articles were already in the file. To write this review, the files were searched by individual topics or groups of topics.

Characteristics of the HFV literature

The major problem encountered at the beginning was the use by some authors of the same material for several publications, without referencing it. This was quite frequent, and a total of 130 articles (mainly abstracts) were deleted from the topics list because their contents had been published more than once. Material from these articles was later published in a total of 192 reports which in 156 cases did not mention the previous publication. Table 9 shows the articles involved, indicating if the previous publication was acknowledged and if major portions of a report were copied literally in

Table 9: Articles from the HFV literature (LATER PUBL.) that have been published previously (PREV. PUBL.), at least in part. For details see text.

PREV. PUBL.	LATER PUBL.	REF.	PREV. PUBL.	LATER PUBL.	REF.
6	54	YES	134	152	NO
7	249	YES	134	129	NO
14	13	NO	134	150	NO
15	13	NO	140	141	NO
24	247	YES	140	247	YES
25	150	NO	141	6	NO
27	29	NO	144	150	YES
28	209	YES	145	152	NO
32	208	NO	145	155	YES
33	441	YES	145	129	NO
37	54	NO	145	150	YES
37	51	NO	146	150	NO
38	54	NO	147	155	NO
38	51	NO	147	134	NO
41	621	NO	147	150	NO
41	622	NO	149	247	YES
41	55	NO	150	152	NO
41	58	YES	150	247	YES
42	51	YES	152	155	NO
42	44	NO	153	154	NO
43	54	YES	153	129	NO*
44	54	YES	153	129	NO*
45	58	YES	153	148	NO*
46	58	YES	161	195	NO
46	57	YES	183	181	NO
46	51	YES	187	151	NO
50	58	NO	194	195	NO
51	54	YES	196	195	NO
54	52	NO	197	199	NO
54	55	NO	198	199	NO
54	58	NO	198	197	NO
54	52	NO	201	202	NO
65	68	NO	203	154	YES
67	68	NO	204	205	NO
80	56	NO	207	277	NO
90	150	NO	212	210	NO
91	219	NO	226	231	NO
103	101	NO	227	231	NO
105	108	NO	228	232	NO
106	30	YES	230	232	YES
107	30	NO	230	232	YES
109	112	NO	231	247	NO
113	110	NO	233	203	NO
117	685	NO	236	235	NO*
118	119	NO	242	247	NO
120	123	NO	242	244	NO
122	123	NO	243	165	NO
129	154	NO	245	247	YES
132	133	NO	259	260	NO

Table 9: (continuation)

PREV. PUBL.	LATER PUBL.	REF.	PREV PUBL.	LATER PUBL.	REF.
268	269	YES	473	474	YES
272	51	NO	477	479	NO
302	603	NO	478	479	YES
302	343	NO	481	377	NO
315	318	NO	486	487	NO
318	316	NO	495	497	NO
322	323	NO	496	498	NO
323	338	YES	500	501	NO
325	326	NO	502	503	YES
325	403	NO	511	512	NO
325	420	NO	614	615	NO
327	420	NO	615	617	NO*
327	328	NO	616	617	NO*
331	334	NO	616	615	NO
331	474	NO	621	55	NO
332	333	NO	622	55	NO
339	402	NO	624	625	NO
343	603	NO	627	628	YES
346	349	NO*	643	646	NO
368	369	NO	644	647	NO
370	371	NO	651	654	NO
373	372	NO	653	652	NO
377	483	NO	657	663	NO
378	399	NO	658	663	NO
384	385	NO	659	663	NO
388	389	NO	660	658	NO
393	130	NO	661	657	NO
398	399	YES	662	706	NO
401	402	NO	663	673	NO
403	420	NO	668	738	NO
403	326	NO	669	671	NO
404	405	NO	672	741	NO
406	408	NO	680	679	NO*
409	410	YES	680	657	NO
413	514	NO	683	681	NO
417	418	NO	716	620	NO
431	348	NO	718	631	YES
432	457	NO	718	610	YES
438	441	NO	726	735	NO
440	441	NO	726	734	NO
440	438	NO	733	685	NO
453	455	NO	736	737	NO
458	460	NO	737	738	NO*
462	479	NO	738	666	NO
466	467	NO	741	685	NO
472	474	YES	764	768	NO

a later publication. In some cases, an article was published again in abbreviated form; in these cases the later publication was also deleted from the computer search list.

Some groups tended to repeat their material, without reference, more than others; for example, the Pittsburg group failed to report previous publications in 76% of the cases (out of 46 instances in which repeated publication of experimental results was detected); the Johns Hopkins group did not report previous publication in 95% of the cases (out of 22 instances of publication of previous material). Sometimes entire paragraphs or even the whole abstract were repeated almost word by word in subsequent publications (for example, Refs.679 and 680; 613 and 611; 32 and 208; 153 and 129). The computer program greatly facilitated the article identification task, which would have been very difficult otherwise.

There are some factors that decrease the scientific value of the HFV literature: the bias shown by some groups (like the Pittsburg and Orebro groups) that tend to emphasize the good side of HFV and overlook the bad side; the abundance of anecdotal human studies without adequate controls; the use of statistical analysis on very small groups of data (for example: Ref.610, n=3; Ref.656, n=4; Ref.609, n=4). The large variation in the circuits and measuring systems used by different groups makes comparisons difficult and may explain the diversity in exerimental findings.

CONCLUSIONS

Despite the widespread use of HFV, there is not a clear picture of how it works, its indications or its dangers. Available data suggest that both convective and diffusion mechanisms are involved in gas exchange during HFV. The only clear indications seem to be laryngeal surgery, ventilation during endoscopy and management of patients with BPF (all with HFJV). There are many reports of prolonged use of HFV in humans, but the long-term effects have not been properly studied, even in animals. Although HFV may never be used as a common ventilatory mode in intensive care, it has become an excellent tool for the study of cardiopulmonary physiology in general and gas exchange in particular.

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CHAPTER 1

GAS EXCHANGE AND CARDIOVASCULAR FUNCTION DURING HIGH FREQUENCY OSCILLATORY VENTILATION

INTRODUCTION

The first set of experiments using HFOV in dogs was designed to characterize the ability of the bellows pump to achieve satisfactory gas exchange. The effects of HFOV on cardiovascular function and oxygen delivery were also assessed. Several frequencies and air flows were used, to assess whether a certain combination was best at achieving good gas exchange. In preliminary trials it was found that a frequency of 10 Hz was usually unable to maintain sufficient gas exchange, consequently it was excluded from the present experiments. When these studies were begun (1980), the importance of $\overline{\text{Paw}}$ and FRC was unknown, and they were not measured in the present experiments. The results obtained stressed the importance of these parameters and further studies were undertaken to characterize them.

MATERIALS AND METHODS

Nine mongrel dogs (7.6 ± 1.2 kg) were studied. The animals were anesthetized with pentobarbital (30 mg/kg) and intubated with a 9 mm i.d. cuffed endotracheal tube. Anesthesia was maintained with supplemental boluses of pentobarbital (1.5 mg/kg) and muscle relaxation was established and maintained with boluses of pancuronium bromide (0.1 mg/kg). A flow-directed thermodilution catheter (7F Instrumentation Laboratory 93A-301) was introduced through a femoral vein into the pulmonary artery. The proximal port was used to infuse a solution of 3.3% dextrose in 0.3% saline at a rate of 4 ml/kg/hr. The distal port was used to measure $\overline{\text{PAP}}$ and PWP (Statham P23Db). A second catheter was introduced through a femoral artery to monitor $\overline{\text{SAP}}$ (Statham P23Db) and obtain samples for blood gas analysis. Also, a minimum of 3 blood samples for hemoglobin measurement were obtained throughout the studies. A plastic catheter (5 mm internal diameter) was inserted into the pleural space through the sixth intercostal space, right midaxillary line, and connected to a differential pressure transducer (Statham PM5) via air-filled tubing, to obtain continuous measurements of Ppl. All pressures during IPPV were measured at end expiration. Transmural values (TM) of CVP, $\overline{PAP}$ and PWP were calculated by subtracting Ppl from the intravascular measurements. $\dot{Q}$ was measured by the thermodilution technique (with 3 ml boluses of ice-cold 5% dextrose solution, by triplicate).

For IPPV, the animals were ventilated with an animal ventilator (Harvard model 607) delivering a tidal volume of 15 ml/kg, at 15 bpm. The animals were also ventilated with the metal bellows HFOV pump with the standard circuit, but without an airway pressure chamber (Fig.1-1). Measurements obtained during IPPV were used as control values and were taken after 15 to 20 minutes of continuous IPPV, before or after each set of measurements on HFOV. Animals could be switched from HFOV to IPPV and vice versa in 3--5 s. For HFOV, the animals were assigned at random to a bias flow of air of 1 or 4 L/min and oscillatory frequencies of 15, 20, 25 and 30 Hz.

Statistical analysis: A Student's paired t-test was used to compare measurements taken during HFOV with corresponding IPPV controls. The control values were obtained five minutes before or 15 minutes after a given HFOV setting. In a few instances, and for various technical reasons, control values could not be obtained. In these cases, a linear regression analysis was performed, with the remaining control values as the dependent variable, and elapsed time as the independent variable.

When the linear correlation coefficient obtained was significant to at least the 5% level, a control value was calculated for the time when it was missed. When there was no significant correlation, the HFOV value lacking a control IPPV value was not used for comparison. The calculated controls were distributed as follows: 1 out of 47 HR values; 2 out of 45 CVP; 4 out of 46 $\overline{\text{PAP}}$, 4 out of 35 $\dot{Q}$; 1 out of 38 PaO_2, and 2 out of 38 $PaCO_2$. The use of calculated control values prompted to a stricter use of significance levels, only p values smaller than 0.025 were considered as significant.

A minimum of five pairs (HFOV vs IPPV) were required for the t-tests. Standard formulas were used to calculate means, standard deviation (SD), and t, obtaining the levels of significance from two tailed tables. A paired t-test was performed with individual measurements, using the values obtained in different dogs at the same levels of HFOV. Each HFOV value was compared with the corresponding IPPV control. Although HFOV measurements lacking controls were not used for the paired t-tests, they were utilized to calculate means and SD.

The values of pH, O_2 saturation and $\dot{Q}s/\dot{Q}t$ were transformed in order to obtain a "normal" distribution (7). The pH values (which are on a log scale) were converted into $[H^+]$(linear scale) according to the formula $[H^+] = 10^{-pH} \times 10^9$. The results were converted back into pH units after the statistical analysis using the inverse calculation $pH = 9 - \log [H^+]$. Also, oxygen saturation and $\dot{Q}s/\dot{Q}t$ values were used for statistical calculations after an angular transformation to avoid skeweness (they are on % scale), according to the formula $x = \arcsin \sqrt{\text{percentage}}$ (7), and the results of the analysis converted back into percentage using: $\% = (\sin x)^2$.

RESULTS

Blood Gases: The results of blood gas data and their statistical analysis are presented in Table 1-1. The PaO_2 values during HFOV were similar to IPPV, except at low frequencies and bias flows during which there was a tendency for lower PaO_2 during HFOV. The oxygen saturation of the arterial blood and arterial pH were similar during HFOV and IPPV. Similar levels of $PaCO_2$ were observed except at low frequencies and bias flows in which there was a trend for higher $PaCO_2$ during HFOV. The relatively high IPPV tidal volumes (and consequently minute volumes) used (60% higher than those reported for spontaneous breathing animals, Ref. 1) and normal rates induced low $PaCO_2$ during IPPV. The measurements obtained from mixed venous samples ($P\bar{v}O_2$, $S\bar{v}O_2$ and $\bar{v}pH$) were slightly lower during HFOV although statistically significant differences were usually not present.

Calculated parameters from blood gas measurements and $\dot{Q}$ are presented in Table 1-2. The values for CaO_2, $P(A-a)O_2$ and $\dot{Q}s/\dot{Q}t$ were similar during IPPV and HFOV. However, mixed venous oxygen content ($C\bar{v}O_2$) and $\dot{V}O_2$ were lower during HFOV at some flows and frequencies. Conversely, $C(a-\bar{v})O_2$ was usually higher during HFOV. However, these differences were generally not statistically significant. O_2Del was usually significantly lower during HFOV (Fig. 1-2).

Hemodynamics: The results obtained from hemodynamic measurements are presented in Table 1-3. HR and $\overline{SAP}$ were similar during HFOV and IPPV at all frequencies and flows, but CVP, $\overline{PAP}$ and PWP were significantly higher during most HFOV frequencies and bias flows (Fig. 1-3). However, when transmural values (TM) were calculated for CVP, $\overline{PAP}$ and PWP (Table

1-4), the differences between HFOV and IPPV were much smaller and not statistically significant. $\dot{Q}$ values were significantly lower during HFOV (Fig. 1-3).

The values for Ppl obtained during the hemodynamic studies are included in Table 1-4. Mean Ppl during HFOV was higher than end-expiratory IPPV values (Fig 1-2), the differences being statistically significant.The variables calculated from the hemodynamic parameters are presented in Table 1-5. Stroke volume (SV) and LVSW were usually lower during HFOV; RVSW was similar during HFOV and IPPV. PVR (Fig. 1-2) and SVR were higher during HFOV, the differences being statistically significant.

Table 1-6 shows the statistical analysis of the linear correlations between parameters obtained during HFOV (at bias flows of 1 and 4 L/min) and frequency. Of the blood gas and derived values, only $S\bar{v}O_2$, $\dot{Q}s/\dot{Q}t$ and O_2Del showed a significant correlation with HFOV frequency (all only at 4 L/min and with negative slope). Several hemodynamic and derived parameters had significant correlation with HFOV frequency at 4 L/min: CVP and PVR (positive slope), and $\overline{SAP}$, $\dot{Q}$, SV and LVSW (negative slope). At 1 L/min only $\dot{Q}$ and SVR had a significant correlation with frequency (with a negative and positive slope, respectively). Ppl was correlated with frequency only at 4 L/min (positive slope).

DISCUSSION

With the use of the metal bellows HFOV pump, normal oxygenation was achieved with good CO_2 elimination even though the tidal volumes were smaller than the dead space (2). The hemodynamic data suggest a depressed left ventricular function with an increased preload, an effect that tended to be more important at the higher frequencies and bias flows. This could be due to a direct effect on the left ventricle like that suggested for PEEP (6), which can not be ruled out in the present study. However, it has also been suggested that at high alveolar pressures, the PWP may be much higher than the left ventricular filling pressure (4). In another study with this HFOV system it was concluded that $\overline{\text{P}}$alv was increased (Chapter 9A). This could induce a vascular-waterfall effect at the alveolar level which would help explain the increased pressures of the pulmonary circulation and high pulmonary vascular resistances. An increased pressure gradient between the "wedge" and left atrium could explain the impaired $\dot{Q}$ by a decreased preload. Another mechanism that could explain the low $\dot{Q}$ with high PWP is a decrease in left-ventricular compliance (5) induced by a high periventricular pressure (secondary to the high intrapumonary pressure). The increased SVR despite a normal $\overline{\text{SAP}}$ was probably due to compensatory vasoconstriction triggered by the decreased $\dot{Q}$. It is surprising that the transmural values for $\overline{\text{PAP}}$ were not significantly different from control despite an increase in PVR. This may be due to the fact that at high lung volumes, perivascular pressures can be lower than Ppl (3), which would make the calculated transmural values incorrect. In the present studies, CVP was obtained from the proximal port of the thermodilution catheter, which was probably situated at the inferior vena cava level. Data from previous studies (Chapter 3) indicated that IVCP is a good estimate of RAP during HFOV, but during IPPV IVCP overestimated RAP by 2.3 mm Hg. If appropiate corrections had been introduced, CVP would probably have been significantly higher during HFOV.

The decreased $\dot{Q}$ was responsible for a decreased oxygen delivery in the presence of normal oxygen concentration of the arterial blood. This stresses the importance of the $\dot{Q}$ measurement to interpret the adequacy of tissue oxygenation.In the present study, peripheral tissues were receiving less oxygen during HFOV despite a normal PaO_2.

In summary it can be concluded that HFOV can impair cardiovascular function and thus decrease oxygen delivery despite normal arterial blood gases.

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Table 1-1: Blood gas values, obtained at different frequencies and bias flows

Parameter		15Hz/1L	20Hz/1L	25Hz/1L	30Hz/1L	15Hz/4L	20Hz/4L	25Hz/4L	30Hz/4L
PaO_2	H	65±14	73±8	77±12	77±9	77±13	77±10	78±12	80±7
(torr)	I	74±3	83±8	81±7	78±7	88±8	78±6	76±11	76±7
		NS	*	NS	NS	NS	NS	NS	NS
SaO_2	H	85±13	92±5	91±6	91±4	91±7	90±5	92±3	92±3
(%)	I	92±1	94±1	93±3	92±2	94±2	93±1	92±4	92±2
		NS	NS	NS	NS	NS	NS	NS	NS
$PaCO_2$	H	37±8	36±6	32±7	31±5	33±8	32±12	30±5	29±5
(torr)	I	30±3	29±1	31±2	30±2	28±4	29±5	30±6	30±3
		NS	NS	NS	NS	NS	NS	NS	NS
apH	H	7.30±0.01	7.39±0.05	7.39±0.05	7.37±0.02	7.38±0.04	7.35±0.04	7.37±0.06	7.32±0.01
	I	7.38±0.04	7.42±0.04	7.42±0.05	7.41±0.04	7.43±0.05	7.39±0.05	7.38±0.08	7.39±0.03
		NS	NS	NS	NS	NS	NS	NS	NS
$P\bar{v}O_2$	H	40±8	41±6	40±4	42±4	39±4	40±6	39±6	38±6
(torr)	I	41±8	44±4	42±7	44±4	43±8	46±8	42±4	42±5
		NS	NS	NS	NS	NS	NS	*	NS
$S\bar{v}O_2$	H	61±19	71±8	68±12	68±6	66±12	66±14	65±16	61±16
(%)	I	67±11	74±4	72±9	70±5	74±7	75±7	71±9	66±7
		NS	NS	NS	NS	*	NS	NS	NS
$\bar{v}pH$	H	7.26±0.01	7.33±0.02	7.33±0.08	7.32±0.05	7.35±0.04	7.31±0.03	7.35±0.07	7.30±0.02
	I	7.33±0.05	7.37±0.05	7.35±0.05	7.33±0.03	7.38±0.06	7.35±0.06	7.37±0.10	7.31±0.04
		NS	*	NS	NS	NS	NS	NS	NS

Values are mean ± SD; 1L & 4L: bias flow 1 & 4 Liters/min; H: HFOV; I: IPPV.

NS: $p>0.025$; *: $0.025>p>0.01$; **: $0.01>p>0.001$; ***: $p<0.001$.

Table 1-2: Parameters Calculated from blood gas and hemodynamic data

Parameter		15Hz/1L	20Hz/1L	25Hz/1L	30Hz/1L	15Hz/4L	20Hz/4L	25Hz/4L	30Hz/4L
CaO_2	H	17.0±3.9	19.6±4.8	17.8±4.6	18.5±4.2	18.2±4.1	18.1±4.3	18.9±4.4	20.0±3.5
(ml/100)	I	18.7±4.3	19.1±3.7	18.7±4.2	19.1±4.6	18.7±4.2	18.5±4.7	18.5±4.9	19.8±3.6
		NS	NS	NS	NS	NS	NS	NS	NS
$C\bar{v}O_2$	H	12.6±4.2	14.0±3.8	13.0±4.5	12.7±3.4	14.4±3.0	13.0±3.2	13.5±4.5	12.9±3.6
(ml/100)	I	14.0±5.3	14.9±3.6	14.1±4.6	13.0±3.5	16.1±4.0	14.9±4.6	14.3±4.2	14.2±3.6
		NS	**	NS	NS	NS	NS	NS	*
$C(a-\bar{v})O_2$	H	4.6±1.3	4.3±1.0	4.4±0.9	4.4±0.8	5.2±1.7	5.0±1.6	5.4±0.9	6.7±2.0
	I	4.8±1.6	4.0±0.7	4.0±1.4	4.1±0.7	4.1±1.6	3.6±1.7	4.2±1.1	4.3±1.2
		NS	NS	NS	NS	*	NS	NS	NS
$P(A-a)O_2$	H	28.3±7.4	27.9±7.8	22.8±7.9	25.1±8.4	21.5±5.4	20.6±8.7	22.9±9.2	21.2±7.5
(torr)	I	25.2±3.6	23.6±9.7	22.5±8.7	25.4±6.0	22.9±6.5	21.9±7.9	25.2±6.7	24.7±5 4
		NS	NS	NS	NS	NS	NS	NS	NS
$\dot{Q}/\dot{Q}t$	H	29±3	11±7	10±10	13±14	16±16	15±13	13±15	9±10
(%)	I	17±7	11±5	12±9	14±8	15±15	20±13	16±10	15±7
NS		NS	NS	NS	NS	NS	NS	NS	NS
$\dot{V}O_2$	H	31.5±11.0	31.5±8.6	33.2±4.6	33.6±7.2	34.8±6.0	37.7±11.8	35.8±9.0	27.0±8.4
(ml/min)	I	43.5±14.7	38.2±8.9	37.5±9.3	40.8±10.0	31.2±9.7	32.2±11.7	34.0±11.0	45.2±12.5
		Δ	NS	NS	**	NS	NS	NS	NS
O_2Del	H	124±42	148±48	136±44	124±29	144±38	139±77	125±36	100±14
(ml/min)	I	164±75	187±68	179±63	172±42	174±57	181±60	153±22	154±28
		Δ	*	*	**	**	*	NS	*

Symbols as in Table 1.Δ: n<5 pairs, no statistical comparison made.

Table 1-3: Hemodynamic parameters, obtained at different frequencies and bias flows

Parameter		15Hz/1L	20Hz/1L	25Hz/1L	30Hz/1L	15Hz/4L	20Hz/4L	25Hz/4L	30Hz/4L
HR	H	156±25	181±28	175±31	177±32	167±23	170±30	175±27	173±33
(b/min)	I	163±32	174±25	166±32	165±30	167±27	170±29	173±30	167±30
		NS	NS	NS	NS	NS	NS	NS	NS
$\overline{SAP}$	H	127±17	137±10	136±12	132±19	133±13	127±10	124±17	114±19
(mm Hg)	I	129±11	135±11	132±13	126±13	132±14	127±11	124±14	135±12
		NS	NS	NS	NS	NS	NS	NS	NS
$\overline{PAP}$	H	22.7±5.3	24.6±7.4	23.9±5.4	26.1±4,6	21.2±5.2	24.9±5.3	27.0±8.0	26.3±3.7
(mm Hg)	I	17.6±4.5	17.9±2.4	16.9±3.5	17.9±2.9	15.9±4.4	17.1±2.8	18.1±7.5	20.3±5.7
		**	*	***	**	**	**	**	**
CVP	H	6.1±3.1	6.7±3.0	6.1±2.0	7.5±2.1	6.2±2.5	6.9±2.0	7.0±2.0	7.8±2.3
(mm Hg)	I	2.7±0.9	2.7±1.3	2.4±1.0	2.8±1.9	2.6±1.1	2.6±0.9	3.1±1.8	2.6±1.1
		*	**	***	***	***	***	***	***
PWP	H	7.6±3.9	10.5±5.1	8.1±3.6	12.2±9.8	8.4±4.1	9.9±5.1	8.3±5.1	12.1±4.8
(mm Hg)	I	4.2±2.5	3.6±2.4	4.0±2.8	6.4±6.3	4 4±2.8	4.9±4.2	4.2±4.6	5.9±5.0
		*	*	***	*	**	**	NS	**
$\dot{Q}$	H	0.77±0.17	0.77±0.20	0.78±0.23	0.72±0.31	0.85±0.26	0.78±0.24	0.67±0.15	0.55±0.15
(L/min)	I	0.93±0.28	1.00±0.27	1.01±0.37	0.98±0.37	0.98±0.32	1.03±0.40	0.87±0.20	0.86±0.28
		NS	**	**	**	**	**	*	*

Symbols as in Table 1.

Table 1-4: Pleural pressures and hemodynamic parameters corrected for transmural pressures (TM)

Parameter		15Hz/1L	20Hz/1L	25Hz/1L	30Hz/1L	15Hz/4L	20Hz/4L	25Hz/4L	30Hz/4L
Ppl	H	-1.3±1.8	-0.6±1.2	0.1±3.2	0.3±1.6	-1.7±2.2	-0.5±1.3	0.1±1.9	0.7±2.0
(cm H_2O)	I	-4.9±2.1	-5.7±0.6	-5.9±1.9	-5.2±1.3	-6.2±1.5	-5.2±1.5	-6.1±1.7	-5.1±1.7
		***	***	***	***	***	***	***	**
$\overline{PAP}$(TM)	H	23.5±4.9	25.4±7.7	23.8±4.6	26.9±4.7	22.8±4.4	23.7±4.3	27.5±7.0	25.8±3.5
(mm Hg)	I	21.3±3.8	22.5±1.6	20.8±5.2	20.0±5.2	19.2±6.0	20.8±3.2	22.2±6.5	24.6±6.0
		NS	NS	NS	NS	NS	NS	NS	NS
CVP(TM)	H	6.9±3.2	7.4±3.1	6.4±1.4	7.3±1.5	6.9±2.4	7.1±2.5	6.7±1.5	7.0±1.9
(mm Hg)	I	6.4±1.1	6.9±1.6	6.7±1.3	6.9±1.6	7.1±0.8	6.7±1.3	7.4±1.8	6.3±1.0
		NS	NS	NS	NS	NS	NS	NS	NS
PWP(TM)	H	8.6±4.1	9.6±5.8	7.8±3.5	8.9±2.7	9.5±4.3	9.8±5.1	8.7±3.0	10.4±3.7
(mm Hg)	I	8.0±2.1	6.8±2.7	7.0±3.8	8.2±2.8	8.2±1.9	8.9±4.2	6.9±4.9	9.7±5.0
		NS	NS	NS	NS	NS	NS	NS	NS

Symbols as in Table 1.

Table 1-5: Parameters calculated from hemodynamic data

Parameter		15Hz/1L	20Hz/1L	25Hz/1L	30Hz/1L	15Hz/4L	20Hz/4L	25Hz/4L	30Hz/4L
SV	H	5.4±1.5	4.5±1.5	4.7±1.5	4.4±2.1	5.3±1.9	4.9±1.5	4.0±1.5	3.6±1.5
$\left(\frac{ml}{beat}\right)$	I	6.4±2.7	5.9±1.8	6.4±1.9	6.4±2.3	6.3±2.3	6.2±2.6	5.5±1.8	5.8±2.6
		NS	**	**	***	NS	*	**	*
LVSW	H	9.6±3.0	8.1±3.1	8.7±2.7	7.9±3.5	9.6±3.5	8.2±3.3	7.2±2.8	4.8±1.3
(gm-M)	I	11.4±4.6	11.0±3.7	12.0±4.0	11.0±4.5	11.0±4.2	11.3±5.4	9.5±3.7	10.4±4.4
		NS	*	*	**	NS	NS	NS	NS
RVSW	H	1.7±0.9	1.5±0.9	1.6±0.7	1.7±0.4	1.6±0.8	1.5±0.6	1.7±0.7	1.3±0.4
(gm-M)	I	1.5±0.9	1.3±0.4	1.5±0.6	1.8±1.0	1.4±0.6	1.5±0.6	1.3±0.6	1.7±0.7
		NS	NS	NS	NS	NS	NS	NS	NS
PVR	H	1515±379	1607±508	1566±288	1947±865	1344±589	1392±268	2100±605	1023±954
$\left(\frac{dyn \times s}{cm^5}\right)$	I	1165±595	1260±728	1076±474	1064±373	1137±943	964±347	1276±571	1312±437
		NS	NS	**	NS	NS	**	**	NS
SVR	H	13664±4568	14788±5243	14369±4163	16179±6198	12977±5192	13040±3146	14396±3188	16256±6536
$\left(\frac{dyn \times s}{cm^5}\right)$	I	12139±5066	11589±4331	11838±4597	11172±4168	11796±5325	10927±3926	12177±4474	13404±4913
		*	***	**	**	NS	**	NS	NS

Symbols as in Table 1.

Table 1-6: Linear correlation of parameters (r values) with HFOV frequency at 1 and 4 L/min bias flow.

Parameter	1 L/min	4 L/min	Parameter	1 L/min	4 L/min
PaO_2	0.91	0.78	HR	0.76	0.80
$PaCO_2$	0.82	0.83	$\overline{SAP}$	0.38	0.98 (**)
apH	0.39	0.71	CVP	0.73	0.96 (**)
SaO_2	0.67	0.69	$\overline{PAP}$	0.86	0.87
$P\bar{v}O_2$	0.39	0.50	PWP	0.74	0.88
$\bar{v}$pH	0.26	0.67	Q	0.95 (*)	0.98 (**)
$S\bar{v}O_2$	0.59	0.97 (**)	SV	0.83	0.99 (***)
CaO_2	0.48	0.83	LVSW	0.86	0.97 (**)
$C\bar{v}O_2$	0.65	0.86	RVSW	0.24	0.48
$C(a-v)O_2$	0.85	0.91	SVR	0.94 (*)	0.76
$P(A-a)O_2$	0.84	0.03	PVR	0.85	0.94 (*)
$\dot{Q}s/\dot{Q}t$	0.77	0.98 (**)	CVP(TM)	0.36	0.65
$\dot{V}O_2$	0.98	0.89	PAP(TM)	0.790	0.80
O_2Del	0.69	0.98 (*)	PWP(TM)	0.12	0.60
Ppl	0.89	0.98 (**)	RVSW(TM)	0.47	0.73

4

Values without symbols: $p>0.025$ (NS); TM: transmural value. Remaining symbols as in Table 1.

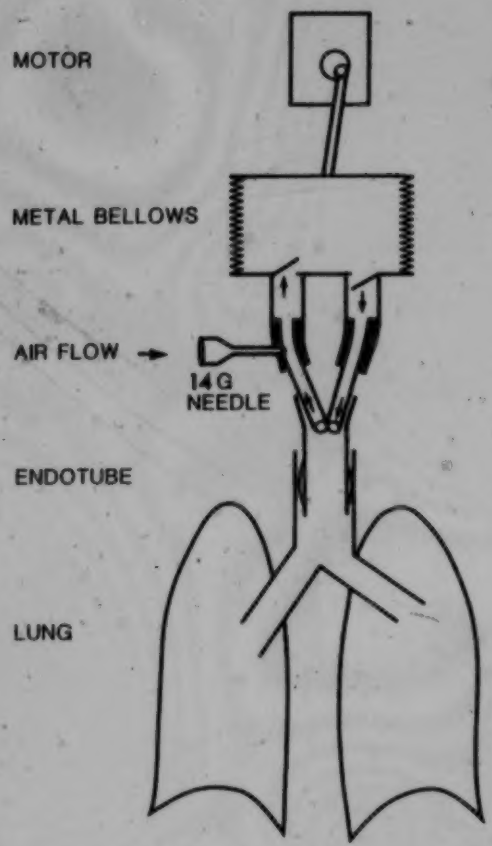
MOTOR
METAL BELLOWS
AIR FLOW
14G NEEDLE
ENDOTUBE
LUNG

Fig. 1-1

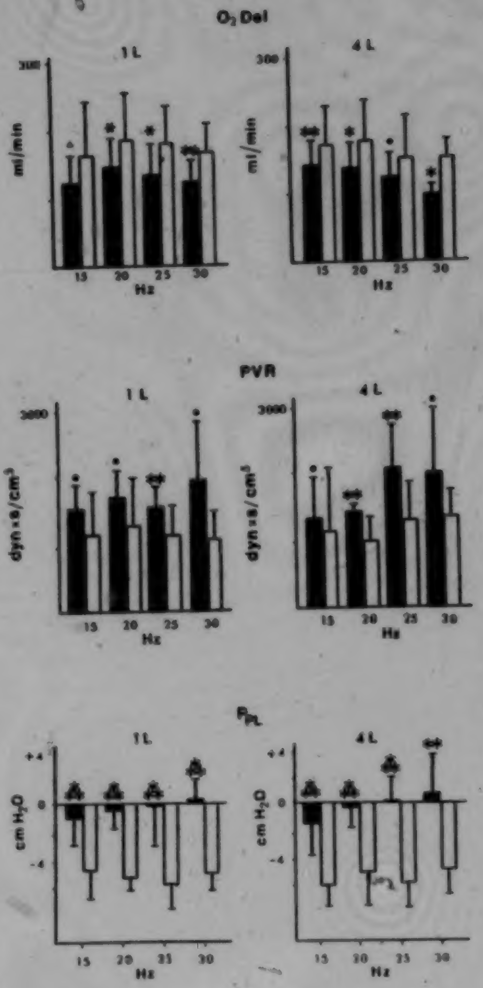

Fig. 1-2

Figure 1-1: Diagram of the HFOV circuit. For details see text.

Figure 1-2: Values for O_2 Del, PVR and Ppl during HFOV (black columns) at different frequencies and air flows. Clear columns, IPPV control values. Means ± SD. Symbols: o = $p > 0.025$; * = $0.025 > p > 0.01$; ** = $0.01 > p > 0.001$; *** = $p < 0.001$; Λ = less than 5 pairs of values (no statistical comparison made).

Fig. 1-3

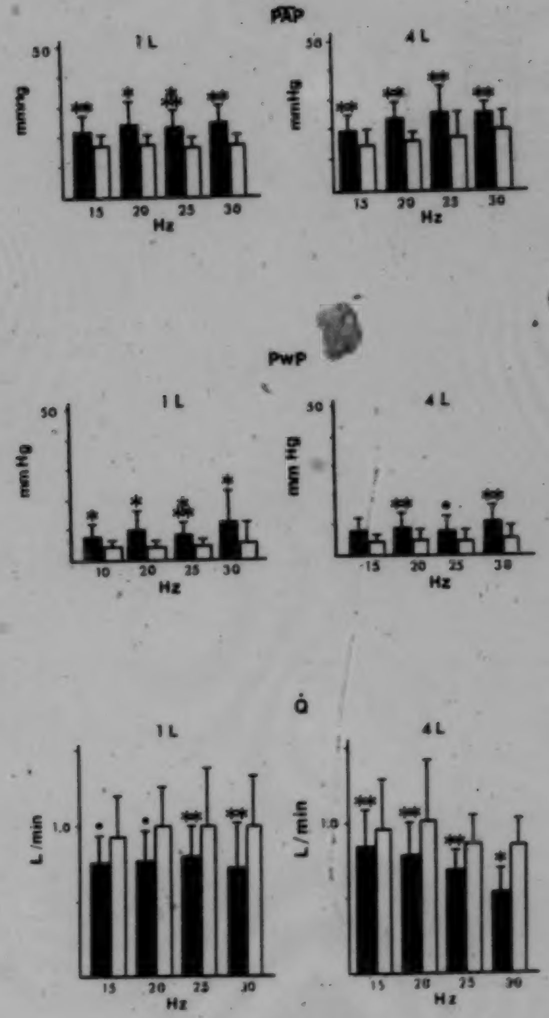

Figure 1-3: Values for $\overline{PAP}$, PWP and $\dot{Q}$ during HFOV (black columns) at different frequencies and air flows. Clear columns, IPPV controls. Symbols as in Fig. 1-2.

CHAPTER 2

ALVEOLAR PRESSURES AND RESTING LUNG VOLUMES DURING HIGH-FREQUENCY OSCILLATION IN DOGS

INTRODUCTION

Available data suggest that, during HFOV, two related variables - FRC and $\bar{P}$alv - are major determinants of the effectiveness of this mode of ventilation in the sick lung(21,23). However, the special characteristics of HFOV make assessment of these parameters technically difficult. For example, proximal $\bar{P}$aw can provide an estimate of $\bar{P}$alv during conventional ventilation, but this may not be true during HFOV: recent data suggest that high-frequency ventilation induces a pressure gradient down the airways, so that $\bar{P}$aw underestimates $\bar{P}$alv(5,19). Furthermore, the most suitable methods for measuring FRC *in vivo* are based on either gas dilution or plethysmography. As most HFOV systems are open, gas-dilution techniques pose major technical problems. Also, as FRC is increased during HFOV(3), the spontaneous respiratory movements that are required to generate pressure/volume changes(9) are delayed or abolished(8), precluding standard plethysmographic measurement of FRC. No other reports on plethysmographic FRC (TGV) measurements during HFOV have been published, the only data from other laboratories having been obtained with gas-dilution methods (for example, Refs. 6,18)

A method for measuring TGV in a body plethysmograph in which the respiratory effort is induced by phrenic-nerve stimulation is described in this chapter. $\bar{P}$alv was estimated from TGV measured during HFOV and the static P/V curves of the respiratory system. In anesthetized dogs, TGV and $\bar{P}$aw were measured before, during, and after HFOV. In a further series of experiments, $\bar{P}$aw, $\bar{P}$pl and changes in FRC were measured at various levels of HFOV.

MATERIALS AND METHODS

Effects of duration of HFOV on lung volumes

Eight dogs (8.8 ± 2.3 kg) were studied. The animals were anesthetized with sodium pentobarbital, 30 mg/kg, and intubated with a cuffed endotracheal tube, 9 mm i.d., 26 cm long. IPPV was instituted with a Harvard ventilator model 607 at a rate of 15 bpm and a V_T of 15 ml/kg. The ETT cuff pressure was kept above 40 cm H_2O. A catheter was inserted into a femoral artery, for monitoring blood pressure and heart rate (via a Statham P23Db transducer) and for withdrawal of samples for blood-gas analysis (analyzer model 816, Instrumentation Laboratory). Another catheter was inserted into a femoral vein, for infusion of a solution of 3.3% dextrose in 0.3% saline (5 ml/kg/hr) and maintenance of anesthesia. The phrenic nerves were instrumented and the dogs placed into a body plethysmograph to measure lung volume by phrenic-nerve stimulation, as described in Appendix III. Core temperature was measured with an intragastric thermistor and maintained at physiologic levels with a water-blanket system.

The animals were also ventilated with the HFOV pump at 20 Hz and 4 L/min bias flow. The circuit used has been described in Chapter 1. For TGV measurements during HFOV, the airway was clamped and the pump stopped at various times after starting HFOV (at 1, 2, 4, 8, 12 and 16 min, assigned at random), and TGV was measured by phrenic-nerve stimulation. Control TGV values were obtained during IPPV, before and after HFOV periods.

Paw was monitored via a side port (3 mm ID) in the Silastic tubing outside the plethysmograph wall. It was displayed, along with arterial blood pressure, on a strip chart recorder (Gould, model 2600S) and was averaged electronically to yield $\bar{P}$aw. The Paw value obtained just after the airway was clamped was termed the occluded airway pressure (Poc). Stress relaxation of the lung causes Paw to decay with time(17) and thus may hamper detection of air-leaks within the system. To test whether a leak existed, the dog's lungs were inflated to a pressure of 25—30 cm H_2O volume and the airway was clamped; the plethysmograph was connected to the bell spirometer with large-bore tubing, and the volume reading was observed for at least 10 sec. Volume remained constant in all cases.

A static P/V curve of the respiratory system was constructed during each control (IPPV) period. First, to obtain a similar volume history for all 8 dogs, the lungs were hyperinflated by the injection of 40—50 ml air/kg and the airway was opened to the atmosphere for 6—10 sec. Then, 5 or 6 different volumes of air were injected into the lungs; Paw was recorded after 3—4 sec equilibration at each volume (modified from Ref.1). The plethysmographic FRC was used to position the P/V curve on the volume axis. The static P/V curves and the FRC measured during HFOV were used to estimate $\bar{P}$alv during HFOV: each FRC value during HFOV was plotted on the P/V curve, and the $\bar{P}$alv value was read off the pressure axis. If the P/V curves obtained before and after HFOV were not identical they were averaged to obtain $\bar{P}$alv.

Effects of variation in HFOV level

For these experiments, another 5 dogs (8.8 ± 2.2 kg) were studied. Anesthesia and intubation were performed and arterial and venous lines inserted as before. A Tygon tube, 3 mm i.d., was inserted into the sixth right intercostal space, to measure Ppl (modified from

Ref.10). Airway and pleural pressures used to construct the static P/V curves of the lungs were measured with two calibrated differential-pressure transducers (Statham model PM5). Water manometers were used for all measurements of $\overline{P}aw$ and $\overline{P}pl$ during HFOV.

The animals were ventilated with IPPV as before, and static P/V curves of the lungs were obtained 10—15 min before and after HFOV. Three curves were plotted(8), for compliance of thoracic cage, lung, and total respiratory system. Eight HFOV levels were studied, twice in each dog, combining at random four frequencies (15, 20, 25 and 30 Hz) and two rates of bias flow of fresh air (1 and 4 liters/min). The HFOV pump circuit described previously was used, but with the HFOV lines and endotracheal tube enclosed in a 290-ml airtight Plexiglass chamber (Fig. 2-1), for measurement of changes in FRC. Fresh air (15 liters/min) was introduced through one side of the chamber, to wash out CO_2. A port in the other side could be connected to a 6-liter bell spirometer (Collins, model 687) or left open into the room. This chamber changed $\overline{P}aw$ by less than 1 cm H_20 and did not alter the blood gases significantly. At each level of HFOV, the animals were ventilated for 3 to 5 min and readings for $\overline{P}aw$ and $\overline{P}pl$ were taken. Then the 15 liter/min flow of air was stopped, and the chamber outlet was connected to the spirometer; this registered a constant volume increment from the flow of air entering the circuit (1 or 4 liters/min). The HFOV pump was turned off 4—6 sec later: this caused FRC to decrease and added to the spirometer a volume (Δ FRC) that was measurable (± 10 ml) as additional to the flow of air that had been entering.

Statistical analysis

For each dog, TGV values measured during IPPV with the helium-dilution technique and phrenic-nerve stimulation were compared, using Student's paired t-test. Differences between TGV values during HFOV were tested with analysis of covariance (20) to correct for baseline TGV. Only the TGV values at 1, 2 and 16 min of HFOV were used, to enhance any possible differences. The values for $\bar{P}$alv estimated from the compliance curves were compared with corresponding values for $\bar{P}$aw, using Student's paired t-test. The data obtained from the experiments at various HFOV levels were not analyzed statistically, due to the small sample size (n=5). Results are reported as mean ± SD.

RESULTS

Effects of duration of HFOV on lung volumes

Lung volume during IPPV averaged 48.8 ± 8.7 ml/kg with the He-dilution technique and 49.9 ± 10.2 ml/kg with phrenic-nerve stimulation (TGV). The difference was not statistically significant ($p>0.05$).

The TGV values reported are those obtained with the phrenic-nerve method. HFOV increased TGV by an average of 63.6% within the first minute and this remained constant for at least the next 15 min (Fig. 2-2). There was no significant difference in TGV values with time during HFOV, or between those measured during IPPV before and after HFOV. Mean airway pressure also remained constant throughout HFOV. Analysis of $\bar{P}$aw vs $\bar{P}$alv derived from the static P/V curves showed the former significantly lower ($p<0.001$) (Table 2-1). In all 5 dogs in which $\bar{P}$aw was monitored when the airway was occluded in preparation for TGV measurement during HFOV, $\bar{P}$aw increased immediately (Poc in Table 2-1) and Poc was between $\bar{P}$aw and calculated $\bar{P}$alv.

Effect of variation in HFOV level

$\bar{P}$aw, $\bar{P}$pl and ΔFRC tended to increase with increasing ventilation frequencies (Fig.2-3), with little difference between the bias flows of 1 and 4 liters/min. $\bar{P}$aw values were in the range of 4.4 to 9.8 cm H_2O; $\bar{P}$pl, -3.0 to +2.0 cm H_2O; and ΔFRC, 32.5 to 180.0 ml.

HFOV did not change the static P/V characteristics of the lungs: the curves constructed before and after the HFOV runs were nearly superimposed except in one dog in which a leftward shift in thoracic-cage compliance was observed. It should be noted that FRC values were not available to correct these curves for absolute volume.

DISCUSSION

Investigation of various methods for measuring the FRC of anesthetized dogs in a plethysmograph (Appendix III) showed induction of the inspiratory effort by phrenic-nerve stimulation the most satisfactory technique for use with HFOV. Considerably less preparation is required if one waits for the animal to take an inspiratory effort against the occluded airway(9) or if the chest is compressed to induce the changes in thoracic volume(4), but neither of these methods would have been suitable for the present experiments. The lung-volume increase induced by HFOV abolishes spontaneous respiration, possibly through a Hering—Breuer reflex(8), for up to 45 sec or even longer. Apnea of this duration would produce hypoxemia before TGV could be measured by the DuBois method. Also, if the respiratory exchange ratio were different from 1.0, TGV would change during this waiting period.

External chest compression(4), the initial method of choice for FRC measurement, consistently yielded higher values than expected. It is likely that the tendency for this method to overestimate TGV is due to the nonuniform changes in lung volume that are produced by localized chest compression; this forces gas into other lung regions, so that proximal airway pressure is an underestimate of the alveolar pressure. Phrenic-nerve stimulation was used, in order to make changes in chest volume more uniform and permit FRC (TGV) measurement during apnea. The airway was clamped during HFOV and then the phrenic nerves were stimulated to generate pressure changes in the lungs within the plethysmograph.

A surprising finding in the present experiments was the achievement of higher lung volumes during HFOV than would be expected for the measured $\overline{P}aw$, suggesting that $\overline{P}alv$ was higher than $\overline{P}aw$ or that lung compliance was increased. In fact, $\overline{P}alv$ derived from P/V curves was significantly higher than $\overline{P}aw$. Also, Poc was consistently higher than $\overline{P}aw$, indicating that pressures were higher distally than at the level of the endotracheal tube. Testing with a sinusoidal pressure wave confirmed accuracy of the system for measuring $\overline{P}aw$. Probably, the aerodynamic characteristics of the respiratory system during HFOV could have created a pressure gradient down the airway. As cross-sectional area increases down the respiratory tree, both gas speed and kinetic energy decrease. According to Bernoulli's equation, a decrease in kinetic energy must be matched by an increase in potential energy, which would result in higher mean pressure(15). The airway pressure gradients are discussed in Chapter 9A.

The consistently raised Poc values were unlikely to be due to an artifact of the occlusion maneuver. Clamping of the airway to measure TGV during HFOV was done manually and without synchronization with the oscillator. It seems inconceivable that the occlusion invariably coincided with end-inspiration during HFOV in an oscillatory cycle that lasted only 0.05 sec. Breen _et al._(5), also, reported Poc higher than Paw in dogs during HFOV and assumed that Poc equalled $\bar{P}$alv. Furthermore, they stated that the venous admixture was similar to that during IPPV only when Poc was 1.5 cm H_2O higher than the IPPV $\bar{P}$alv value. These findings suggest that their measurement of Poc underestimated $\bar{P}$alv by an amount similar to what was observed in the present experiments, in which $\bar{P}$alv - Poc averaged 1.9 cm H_2O.

There could be other explanations for the discrepancy between $\bar{P}$aw and $\bar{P}$alv values. $\bar{P}$alv was derived from TGV measured during HFOV and the static P/V curve of the respiratory system, assuming the same compliance during HFOV and apnea. However, if compliance of the respiratory system were higher during HFOV, lower $\bar{P}$aw could be achieved with the same TGV. Increased thoracic-cage compliance could produce this, but vibration tends to increase muscular tone(14), stiffening the thoracic cage. Increased surfactant activity during HFOV could increase lung compliance, but Frantz _et al._(11) found no change in surface activity of the lung during high-frequency ventilation. In either case, $\bar{P}$oc would not be larger than $\bar{P}$aw. A hysteresis effect, the lung being on the deflation part of the P/V curve, could also explain the lower $\bar{P}$aw during HFOV -- but, again, $\bar{P}$oc would not be higher than $\bar{P}$aw. Moreover, although increased compliance could have caused overestimation of $\bar{P}$alv, it could not have accounted for the increase in $\bar{P}$aw after occlusion of the airway. Therefore, it can be postulated, as Simon *et al.*(19) and Breen *et al.*(5) did, that $\bar{P}$alv is truly higher than $\bar{P}$aw during HFOV, causing larger values for FRC than might be expected from $\bar{P}$aw measurements.

It is clear that HFOV increased FRC, as well as $\bar{P}$aw, $\bar{P}$pl, and $\bar{P}$alv. These changes occurred within 1 min of the start of HFOV and remained stable for at least 15 min. Over a longer period, these pressures and volumes may remain steady unless structural changes occur in the lung parenchyma. As discussed in Chapter 1, the use of a catheter for Ppl mesurement probably induces an artifact in the readings. Therefore the absolute $\bar{P}$pl values reported might not reflect acutal Ppl. However, this artifact was probably constant throughout the experiments with the shape of $\bar{P}$pl changes remaining unaffected. The Ppl values were not used to estimate Palv.

There is wide variation in the design of circuits for high-frequency ventilation(12). Thus their aerodynamic characteristics are likely to vary, giving rise to different effects on the cardiopulmonary system. The changes in lung volume and alveolar and pleural pressures observed during HFOV may be a cause of the decreased cardiac output found by some authors during high-frequency ventilation(3,7; see also Introduction) the increased FRC and alveolar pressure may augment pulmonary vascular resistance(22), and the increased intrapleural pressure may decrease both venous return and left ventricular compliance(16).

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TABLE 2-1: Mean airway pressure ($\overline{P}aw$), airway occluded pressure (Poc) and calculated mean alveolar pressure $\overline{P}alv$ during high-frequency oscillatory ventilation.

Dog no.	$\overline{P}aw$	Poc	$\overline{P}alv$
1	10.7 ± 0.2	12.1 ± 0.5	12.4 ± 0.9
2	9.9 ± 0.1	12.3 ± 0.4	14.5 ± 0.8
3	10.0 ± 0.3	11.5 ± 0.6	13.6 ± 2.1
4	9.9 ± 0.4	12.1 ± 0.4	15.2 ± 0.7
5	9.6 ± 0.3	11.9 ± 0.4	13.9 ± 1.3
6	7.1 ± 0.7	-	10.8 ± 0.7
7	9.4 ± 0.3	-	10.8 ± 0.6
8	6.7 ± 0.1	-	8.0 ± 1.5

Values are means ± SD (n=6), in cm H_2O.

Fig. 2-1

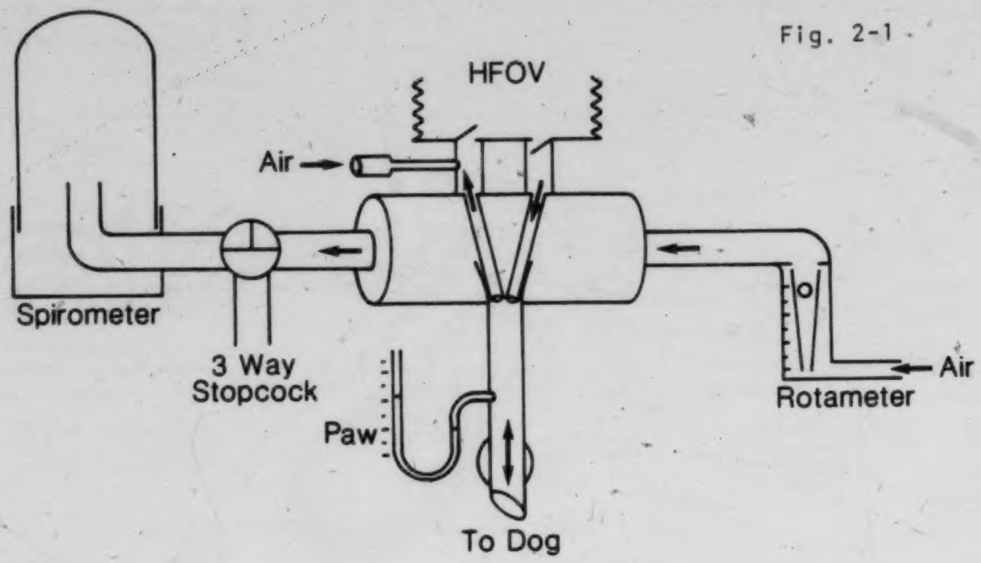
HFOV
Air
Spirometer
3 Way
Stopcock
Paw
To Dog
Rotameter
Air

Fig. 2-2

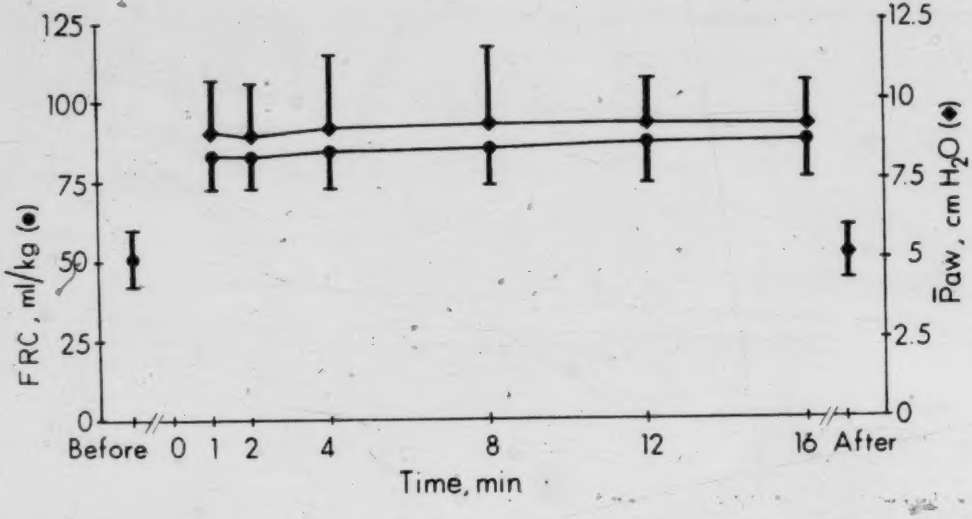

Figure 2-1: Schematic diagram of the modified circuit used for measuring ΔFRC. Figure 2-2: Thoracic gas volumes (FRC) and proximal airway pressure ($\overline{P}aw$) at various times after starting HFOV, and resting volumes during apnea before and after the HFOV measurements. Values are means ± SD.

Fig. 2-3

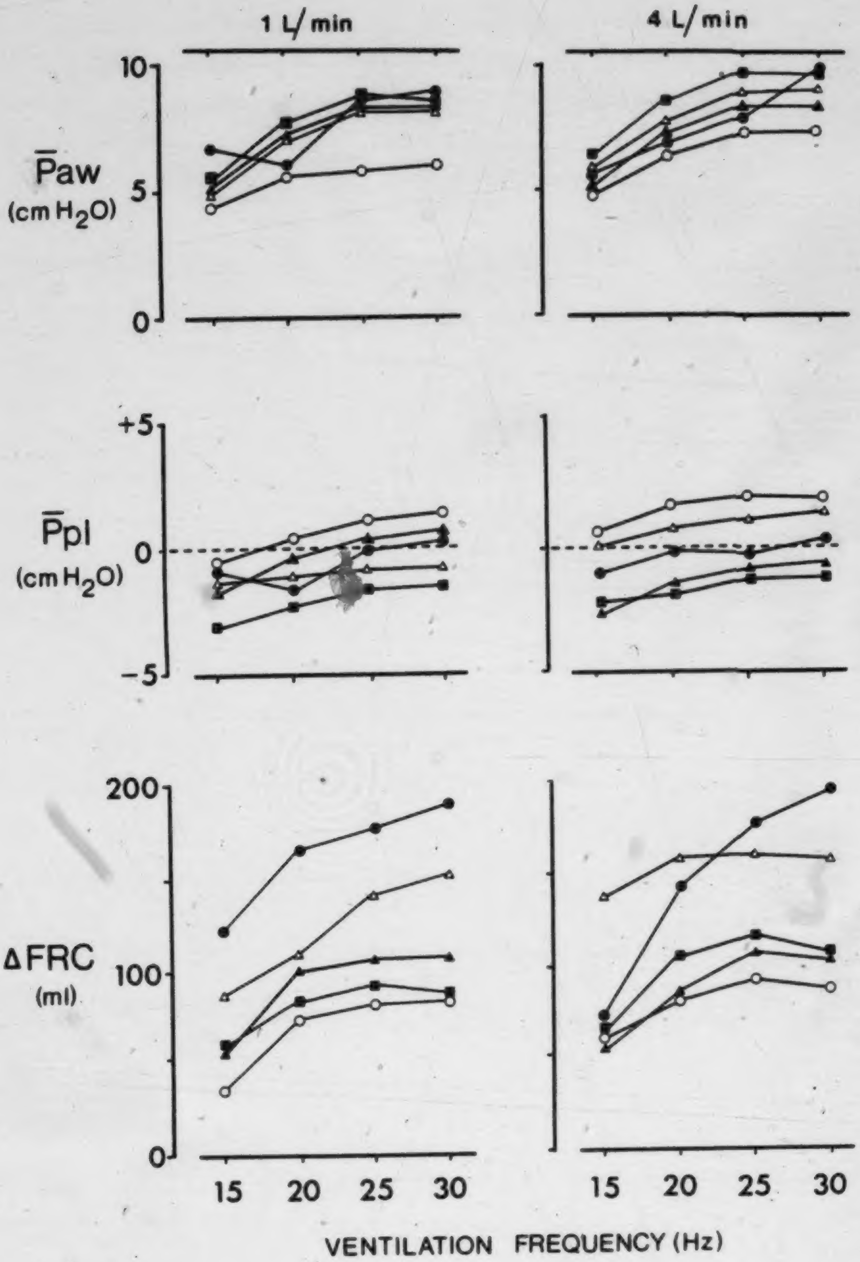

Figure 2-3: Individual data on 5 dogs, showing the effect of various HFOV frequencies on mean airway pressure ($\overline{P}aw$), mean pleural pressure ($\overline{P}pl$), and change in FRC (ΔFRC), at two rates of bias-flow of air (1 and 4 liters/min).

CHAPTER 3

COMPARING LUNG VOLUME AND ALVEOLAR PRESSURE DURING HFOV AND PEEP

INTRODUCTION

Review of the HFV literature reveals a large variation in results and conclusions on the effects of HFV which could be due, at least in part, to the variability in $\overline{P}$alv and resting lung volumes induced by different HFV systems. In Chapter 1, a significant difference in hemodynamic parameters was observed between IPPV and HFOV, but $\overline{P}$alv (or $\overline{P}$aw) and $\overline{V}_L$ were not monitored, and as can be appreciated from Chapter 2, they are altered by HFOV, depending on frequency and bias flow. The present study was undertaken to assess the relative importance of $\overline{P}$aw (and $\overline{P}$alv) and $\overline{V}_L$ in producing the differences between IPPV (with or without PEEP) and HFOV. For this, dogs were ventilated with IPPV, HFOV, and PEEP that induced an end-expiratory lung volume similar to $\overline{V}_L$ during HFOV (hemodynamic parameters were measured at end-expiration), and PEEP that induced a $\overline{P}$d like that seen during HFOV.

MATERIALS AND METHODS

Eight mongrel dogs (7.7 ± 1.3 kg) were anesthetized with pentobarbital sodium (30 mg/kg) and intubated with a cuffed endotracheal tube 9 mm i.d.; cuff pressure was kept above 40 cm H_2O. The animals were ventilated with a Harvard respirator (model 607) delivering a V_T of 15 ml/kg at a rate of 15 bpm; the ventilator's expiratory line was immersed in water to induce a PEEP level of 3 cm H_2O. A 7F flow-directed thermodilution catheter was inserted through a femoral vein and its tip positioned in the pulmonary artery; the proximal port was used to measure IVCP, to maintain anesthesia with pentobarbital boluses and infuse a solution of 3.3% dextrose in 0.3% saline (4 ml/kg/h). Polyethylene catheters (PE90) were introduced through each of the remaining femoral vessels and their tips positioned into the right atrium, abdominal aorta and left ventricle respectively. Samples for blood gas analysis (Instrumentation Laboratory analyzer model 813) were obtained from the aortic catheter. Aortic and left ventricular pressures were monitored with a miniature transducer (Statham model P50), and the remaining vascular pressures with a Statham P23Db transducer. The phrenic nerves were isolated and connected to a Grass stimulator (model SD9), and the animal was placed in a 100-liter airtight Plexiglass box which acted as a plethysmograph (Fig.3-1). Box pressure was monitored with a MP45 Validyne differential-pressure transducer connected to an amplifier, with the output fed into the X axis of an X-Y recorder (model 815M; MFE Corp., Salem, NH). Large-bore tubing connected the box to a 9-liter bell spirometer (Collins model 6001) with a linear-displacement transducer (Sanborn model 575-DT250) attached; changes in position of the bell were displayed numerically on a digital voltmeter (Fluke model 8025B, Everett, WA), to monitor changes in FRC. For plethysmographic FRC measurements, the spirometer tubing was clamped. A polyethylene catheter (PE90) connected to a P300 Validyne transducer, was inserted through an airtight opening in the ETT connector and its tip positioned in the small airways in a position 3—5 cm proximal to the position where wedging occurred. The distal tip of the catheter was occluded and had 6 side holes drilled in its last 15 mm; the catheter was used to monitor $\bar{P}d$. A short catheter with a Validyne MP45 transducer attached was used to obtain Paw for FRC measurement, 4 cm from the proximal airway opening. The amplified transducer output was fed into the Y axis of the X-Y recorder for FRC calculation. A physiological recorder (Gould model 2600S) was used to display cardiovascular pressures, Pd, changes in spirometer volume and, in several cases, pulmonary artery temperature (during $\dot{Q}$ measurements).

When preparation was completed, the animal was placed in the box, the lid was closed, PEEP was set at zero and the respirator rate was adjusted to induce a $PaCO_2$ between 28 and 34 mm Hg. Afterwards, PEEP was reset to 3 cm H_2O. When the box temperature had equilibrated (in approximately 1 hour), the control IPPV period was started by setting PEEP to zero. Fifteen minutes later an arterial sample for blood gas (and hemoglobin) analysis was taken, and the following hemodynamic parameters measured: SAP, PAP, PWP, RAP, IVCP, LVEDP, dP/dt, HR and $\dot{Q}$ (thermodilution, with 3 ml boluses and measured in triplicate). The same measurements were repeated after 15 min on HFOV, PEEP at an $\overline{V}_L$ similar to that induced by HFOV and PEEP at the same $\overline{Pd}$ as obtained during HFOV (see below). When these parameters had been obtained after 15 min of IPPV, FRC was measured as follows: the airway and spirometer tubing were clamped and both phrenic nerves were stimulated simultaneously with a train of 50-Hz impulses of 2-ms pulse duration. Inspiratory efforts were induced by varying the voltage manually from below to above threshold. The slope of at least four X-Y recorder tracings was used to calculate FRC by the method of DuBois (3). The airway was occluded for 30—60 s to complete the FRC measurements. After the FRC measurements, IPPV was continued for another 5 min but at a slightly faster rate (22—25 bpm) to speed the return of blood gases to the pre-measurement levels. After this IPPV period, the HFOV pump was started and the animals ventilated at 20 Hz and 4 L/min of bias flow (see Chapter 1 for a description of the HFOV circuit). The change in resting lung volume induced by HFOV was recorded (this volume, added to baseline FRC corresponded to the average lung volume or $\overline{V}_L$ during HFOV). When the corresponding hemodynamic and gas measurements had been taken (after 15 min on HFOV), the Harvard respirator was again connected and the animals ventilated at the same rate as during control IPPV, but PEEP was added (in 6—10 breaths) until the end-expiratory spirometer reading (from the digital display voltmeter) coincided with the value at the end of HFOV; this ventilation period was named PEEP-V. Fifteen minutes later blood gas analysis and hemodynamic parameters were measured, but this time at end-expiration (for $\dot{Q}$, the ventilator was stopped for 20—30 s to inject the cold solution). After this period, the PEEP level was readjusted, to induce the same $\overline{P}d$ as obtained during HFOV (PEEP-P period). After 15 minutes an arterial blood sample was taken and hemodynamic measurements repeated. Then the airway and spirometer tubing were clamped at end-expiration, and FRC measured again as described before.

To obtain average lung volume ($\overline{V}_L$) during IPPV and PEEP-P, the mean change in volume induced by V_T (calculated from the area of the tracings of spirometer volume changes) was added to the measured FRC. The dP/dt values were obtained directly from left ventricular pressure (Gould Pressure Processor module, model 13-4615-52). Parameters derived from hemodynamic and blood gas data were calculated using standard formulas.

Statistical analysis: Student's two-tailed paired t-tests were used to compare the measurements made on each ventilatory mode with similar data obtained during the other types of ventilation. The significance of the differences IVCP-RAP and PWP-LVEDP during each type of ventilation were also tested with a paired t-test. Tables show average differences between parameters obtained during two test periods. Symbols in figures refer only to comparison between HFOV and other test periods. Data are expressed as mean ± SD, and significance levels were set at $p<0.05$.

RESULTS

Table 3-1 shows the statistical analysis of the differences in hemodynamic parameters, induced by the various ventilatory settings. Table 3-2 shows differences in blood-gas related parameters. $\overline{Pd}$ was significantly lower during IPPV, and HFOV induced higher $\overline{Pd}$ levels than PEEP-V (Fig.3-2) but almost identical to PEEP-P (as required by the protocol). $\overline{V}_L$ was significantly higher during HFOV than during IPPV, but significantly lower than during PEEP-P (Fig.3-3); the experimental setup was designed to induce similar $\overline{V}_L$ during HFOV and PEEP-V, but this could not be tested due to the experimental design. HFOV and PEEP-P induced similar changes in the remaining parameters, except $\dot{Q}$ (Fig.3-4) and O_2Del (Fig.3-5) that were significantly lower during PEEP-P than during HFOV. When compared to PEEP-V, HFOV induced significantly higher $\overline{PAP}$ (Fig.3-6), PVR (Fig.3-7), PWP (Fig.3-8), LVEDP (Fig.3-9) and SVR, but lower $\dot{Q}$ (Fig.3-4) and O_2Del (Fig.3-5). The remaining parameters were similar, including the differences PWP-LVEDP (Fig.3-10) and IVCP-RAP (Fig.3-11). When compared to IPPV, HFOV induced significantly higher $\overline{PAP}$ (Fig.3-6), PVR (Fig.3-7), PWP (Fig.3-8), LVEDP (Fig.3-9), SVR and RAP, but lower $\dot{Q}$ (Fig.3-4), O_2Del (Fig.3-5), LVSW and SV. When PEEP-V was compared to PEEP-P, it induced lower $\overline{Pd}$, $\overline{PAP}$, PVR and $\overline{SAP}$. When compared to IPPV, PEEP-V induced higher $\overline{Pd}$, LVEDP and RAP, but lower $\dot{Q}$, O_2Del, SV, LVSW and IVCP-RAP differences. Finally, when PEEP-P was compared to IPPV, it induced higher $\overline{Pd}$, $\overline{V}_L$, $\overline{PAP}$, PVR, PWP, LVEDP and

SVR, but lower $\dot{Q}$, O_2Del, SV and LVSW.

Table 3-3 shows the statistical analysis of the differences RAP-IVCP and PWP-LVEDP, on each ventilatory mode (see also Figs.3-10 and 3-11). During IPPV, IVCP overestimated RAP by an average of over 2 mm Hg; PWP generally overestimated LVEDP, but the differences were small (average less than 1 mm Hg).

DISCUSSION

The present experiments were designed to match during IPPV, the $\overline{P}$alv and $\overline{V}_L$ levels induced by HFOV. When these parameters were obtained during HFOV, care was taken to avoid high-frequency related measuring artifacts. FRC was measured immediately before starting HFOV, and the subsequent changes monitored continuously. In previous experiments (Chapter 2), it was found that HFOV-related $\overline{V}_L$ changes were established in less than 1 minute, and thus they could be measured with the plethysmograph-spirometer system before fluctuations in box temperature could induce an error in the volume readings (it was observed that spontaneous fluctuations in spirometer readings over 3—4 min periods were negligible). To obtain $\overline{V}_L$ during PEEP-V, FRC was obtained as during IPPV, by phrenic-nerve stimulation; the average volume changes induced by V_T were assessed from the spirometer tracings, to obviate the effects of gas compression on V_T. The high-frequency fluctuations in $\overline{V}_L$ during HFOV, induced by V_T, must have been quite small (less than ± 3 ml/kg, calculated from HFOV V_T; Appendix I). The experiments were designed to match $\overline{P}$d and $\overline{V}_L$, and randomization was not possible; but little change could be expected in the animal preparation over the test periods (maximum 90 min). Results of previous experiments (Chapter 2) and other authors's reports suggest that HFOV induces no change in the P/V characteristics of the lungs (4,10) and if anything chest wall compliance decreases slightly during ventilation (5).

Airway presures were measured in a small airway (Pd), to obtain a close estimate of $\overline{P}$alv and obviate most of the effect of $\overline{P}$aw gradients (see Chapter 9A). The data discussed in Chapter 6 suggest that $\overline{P}$d obtained by the method used in the present study, is a good estimate of $\overline{P}$alv. The $\overline{P}$d-measuring catheter had the tip occluded and 6 terminal side holes to avoid gas velocity-related artifacts in pressure measurment (2).

The results of the present experiments suggest that to induce the same $\overline{V}_L$ as during HFOV, lower $\overline{P}$d is needed during PEEP-V (average 2.5 cm H_2O), and that higher $\overline{V}_L$ (average 5.2 ml/kg) is obtained at similar $\overline{P}$d (PEEP-P). There are two HFV-related effects that could help explain this discrepancy: decreased chest wall compliance and uneven distension of the lungs. HFOV could induce an increase in respiratory muscle tone and shift the P/V curve to the left (see Chapter 2 and Ref.5) causing a higher $\overline{P}$d for the same $\overline{V}_L$, and lower $\overline{V}_L$ for same $\overline{P}$d; however, available data suggest that this effect is small or nonexistent. Also, the airway pressure gradients induced by HFOV (Chapter 9A) imply that the portions of the respiratory tree proximal to the $\overline{P}$d-measuring catheter, are subjected to a distending pressure lower than $\overline{P}$d; during PEEP, the mean pressure in the airways can be expected to be uniform, and equal to $\overline{P}$d. Thus, to obtain the same overall lung (including airways) distension ($\overline{V}_L$) a slightly higher distending pressure ($\overline{P}$d) would be needed during HFOV. Moreover, as discussed in Chapter 9A, one of the major factors responsible for the airway pressure gradients is probably the decrease in gas speed induced by the increase in total crossectional area (through a Bernoulli phenomenon). Due to the anatomy of the dog's airways, the tip of the $\overline{P}$d catheter can be expected to have been located in the lower lobes most of the times, following the longer, more direct bronchial paths; however a large fraction of alveoli are supplied by shorter airways (9). It can be postulated that gas molecules reach alveoli that are close to the carina before a large drop in velocity (and kinetic energy) has occurred; the opposite could be true for alveoli with long bronchial paths, like those in the lower lobes. If this is correct, alveoli close to the carina would be less distended (lower $\overline{P}$alv) than those further away (like those near the tip of the $\overline{P}$d catheter), and total lung volume would likely be below what would be expected if $\overline{P}$alv was uniform throughout the lung. During PEEP-V, the Bernoulli effect can be expected to be minimal and $\overline{P}$alv more uniform, and lower $\overline{P}$d would be needed to obtain a $\overline{V}_L$ like that of HFOV. Similarly, at equivalent $\overline{P}$d (PEEP-P), $\overline{V}_L$ would be lower during HFOV due to insufficient distension of short-airway alveoli. The decreased ventilation of apical regions during HFV, suggested by some reports (1) could be related to the decreased distension of alveoli with short airways. And finally, it can be postulated that, although during conventional ventilation inertia of the lung parenchyma is negligible this may not be the case during HFV (7), thus explaining the higher $\overline{P}$d (necessary to overcome the inertia of lung structures). However none of these factors alone seems to be able to explain the substantial differences in $\overline{P}$d and $\overline{V}_L$ observed in the present experiments, which are probably due to a combination of factors.

In another set of experiments (Chapter 6) it was found that $\overline{P}$d corresponded to the mid-point between the inflation and deflation limbs of the P/V curve of the respiratory system. The discrepancy with the present results can be explained by a different volume history: in those experiments, the lungs had been distended by a sigh maneuver to close to total lung capacity (TLC), which probably moved the HFOV-P/V curve to the left; in the present experiments no sigh maneuver was applied, and the animals were probably ventilated on a less advantageous position of the P/V curve.

In the present study, rather small differences between HFOV, PEEP-V and PEEP-P were anticipated. The overuse of paired t-tests (6 per parameter) instead of one ANOVA test, was thus justified by the necessity to detect small differences. In some cases, the anticipated differences between ventilatory modes were not significant probably due to rather large SD (for example, RAP in HFOV/IPPV, PWP in PEEP-V/IPPV, SVR in PEEP-V/IPPV, and PWP-LVEDP during PEEP-V).

The end-expiratory measurements during PEEP-V were intended to represent data obtained at the same $\overline{V}_L$ as during HFOV. Most likely this was not the case for blood gas data in the present experiments; however, even during IPPV the differences with HFOV were not significant (except for O_2Del). Hemodynamic parameters were measured at end-expiration and cold injections for $\dot{Q}$ measurement were done during apnea (and the respirator stopped until the temperature in the pulmonary artery, monitored in the strip-chart recorder, was close to pre-injection levels). But the expiratory time (apnea during $\dot{Q}$ measurements) was probably not long enough to reach an equilibrium state representative of the end-expiratory lung volume, and the data obtained might have underestimated steady state levels. If this was the case, the differences between HFOV and PEEP-V would have been even larger (Table 3-1).

The overall blood gas data analysis shows that the four ventilatory modes were equally effective (Table 3-2), and the significant decrease in O_2Del was related to the drop in $\dot{Q}$ (Table 3-1) rather than CaO_2. The hemodynamic data indicate that PEEP-P had an effect equivalent to HFOV (except for $\dot{Q}$ and probably vascular resistances), PEEP-V induced less changes than HFOV, and IPPV was the least detrimental for the cardiopulmonary circulation. The fact that at the same $\overline{V}_L$ PEEP-V had less effect, and at equal $\overline{Pd}$, PEEP-P was similar to HFOV, suggests that intrapulmonary pressure is more important than lung volume in determining the cardiovascular effects of HFOV. The increases of PWP above IPPV levels, were followed by similar changes in LVEDP and the gradient PWP-LVEDP remained almost constant (Fig.3-9) which indicates that during HFOV PWP is a good index of LVEDP; the differences PWP-LVEDP, although significant, were minimal and probably unimportant physiologically (less than 1 mm Hg, Table 3-3). However the increases in $\overline{PAP}$ were higher than the increases in LVEDP (Table 3-1), and this suggests that another factor, probably the distension and compression of the pulmonary vessels (12), was also responsible for the increase in PVR. The present data (Table 3-3) also suggest that during HFOV and PEEP, IVCP (measured from the proximal port of a flow-directed catheter in a relatively small animal) is an acceptable estimate of RAP (mean differences < 1 mm Hg, non-significant); however during IPPV IVCP overestimates RAP (mean 2.3 mm Hg, $p<0.05$). These data are important to interpret some of the results of Chapter 1 in which RAP was estimated from IVCP.

The present results show a decrease in $\dot{Q}$ despite an increase in left ventricular (LV) preload, which suggests that the impairment in LV function was due to a decreased LV compliance (8); there was not an increase in preload that could explain the decreased LV function. Also, dP/dt did not change significantly, consequently myocardial depression was unlikely. Right ventricular afterload (with displacement of the interventricular septum) could also have contributed to the decrease in $\dot{Q}$ (11). The increase in SVR was probably due to a baroreceptor-mediated reflex that maintained or increased $\overline{SAP}$ despite a decrease in $\dot{Q}$ (6).

In conclusion, during HFOV, $\overline{P}d$ seems to be a determinant of cardiovascular function and is more important than $\overline{V}_L$. When animals are ventilated with HFOV without a sigh maneuver, a higher $\overline{P}d$ is needed to obtain a $\overline{V}_L$ similar to PEEP.

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TABLE 3-1: Stastical analysis of changes in hemodynamic parameters

	HFOV minus PEEP-V	HFOV minus PEEP-P	HFOV minus IPPV	PEEP-V minus PEEP-P	PEEP-V minus IPPV	PEEP-P minus IPPV
$\overline{Pd}$	2.5±1.4	0.1±0.1	6.4±0.4	-2.5±1.3	3.8±1.3	6.4±0.4
cm H_2O	**	NS	***	**	***	***
$\overline{V}_L$	--	5.2±4.7	20.4±9.4	--	--	25.6±8.8
ml/kg		*	***			***
HR	0.7±7.4	-5.1±10.1	-0.5±11.4	4.8±6.9	0.2±15.4	4.6±17.3
b/min	NS	NS	NS	NS	NS	NS
$\overline{SAP}$	3.0±5.8	-2.9±4.8	-0.4±8.4	-5.9±2.5	-3.4±4.8	2.5±4.8
mm Hg	NS	NS	NS	***	NS	NS
RAP	-0.3±0.8	-0.2±1.2	2.1±2.0	0.1±1.5	2.4±2.1	2.3±1.4
mm Hg	NS	NS	NS	NS	*	**
IVCP	0.1±0.3	-0.3±1.6	0.9±1.9	-0.4±1.5	0.8±1.9	1.2±2.2
mm Hg	NS	NS	NS	NS	NS	NS
ΔIVCP	0.4±7.8	-0.1±1.1	-1.2±1.7	-0.6±1.2	-1.6±1.6	-1.1±1.5
mm Hg	NS	NS	NS	NS	*	NS
$\overline{PAP}$	2.4±2.1	-0.3±2.3	4.2±2.5	-2.7±2.3	1.8±3.1	4.5±2.2
mm Hg	*	NS	**	*	NS	***
PWP	1.3±1.0	1.3±2.0	2.9±2.8	0.1±1.4	1.7±2.3	1.7±1.4
mm Hg	**	NS	*	NS	NS	*
LVEDP	1.6±0.8	1.1±1.9	3.1±2.1	-0.5±1.3	1.5±1.7	2.0±1.1
mm Hg	***	NS	**	NS	*	**
ΔLVEDP	-0.2±0.8	0.2±0.5	-0.1±1.1	0.5±0.7	0.1±1.5	-0.4±1.0
mm Hg	NS	NS	NS	NS	NS	NS
$\dot{Q}$	-63±67	-94±86	-250±219	-31±51	-187±208	-156±162
ml/min	*	*	*	NS	*	*
dP/dt	1.1±2.5	-0.3±2.9	-0.3±4.7	-1.3±4.2	-1.3±4.6	-0.1±5.7
mm Hg/s	NS	NS	NS	NS	NS	NS
SV	-0.4±0.6	-0.4±0.7	-1.6±1.0	-0.0±0.4	-1.2±1.1	-1.2±1.8
ml/b	NS	NS	**	NS	*	**
LVSW	-0.4±1.0	-1.0±1,6	-2.7±2.3	-0.5±0.9	-2.3±1.1	-1.2±0.8
gm•M	NS	NS	*	NS	*	*
RVSW	0.1±0.2	-0.1±0.3	-0.1±0.4	-0.2±0.2	-0.1±0.4	-1.0±1.4
gm•M	NS	NS	NS	NS	NS	NS
SVR	1280±1448	1034±1603	2343±1406	-245±634	1063±1447	1304±1222
dyn•s/cm^5	*	NS	**	NS	NS	*
PVR	181±157	-38±192	339±196	-219±187	158±199	377±199
dyn•s/cm^5	*	NS	**	*	NS	**

NS: $p>0.05$; *: $0.05>p>0.01$; **: $0.01>p>0.001$; ***: $p<0.001$

TABLE 3-2: Statistical analysis of changes in blood-gas related parameters

	HFOV minus PEEP-V	HFOV minus PEEP-P	HFOV minus IPPV	PEEP-V minus PEEP-P	PEEP-V minus IPPV	PEEP-P minus IPPV
PaO_2 torr	-1.5±8.9 NS	-0.3±8.8 NS	-0.4±11.2 NS	1.2±3.6 NS	1.1±6.4 NS	-0.1±6.5 NS
SaO_2 %	0.5±1.9 NS	0.5±1.7 NS	0.1±2.0 NS	0.1±0.5 NS	-0.3±1.3 NS	-0.4±1.3 NS
CaO_2 ml/100	0.1±0.4 NS	0.1±0.4 NS	0.0±0.5 NS	0.0±0.1 NS	-0.1±0.3 NS	-0.1±0.3 NS
$P(A-a)O_2$ torr	2.6±4.1 NS	2.2±4.1 NS	1.3±7.1 NS	-0.4±0.8 NS	-1.3±5.7 NS	-1.0±5.5 NS
O_2Del ml/min	-11±12 *	-16±18 *	-49±39 *	-4±11 NS	-37±38 *	-32±29 *
$PaCO_2$ torr	-1.5±3.9 NS	-2.1±4.8 NS	-0.6±3.2 NS	-0.6±1.9 NS	0.9±2.9 NS	1.4±3.9 NS

TABLE 3-3: Pressure gradients RAP-IVCP and PWP-LVEDP

	IPPV	HFOV	PEEP-V	PEEP-P
RAP-IVCP mm Hg	-2.3±1.4 **	0.9±1.2 NS	0.5±0.9 NS	1.0±1.2 NS
PWP-LVEDP mm Hg	0.9±0.9 *	0.7±0.6 *	0.9±1.1 NS	0.5±0.4 *

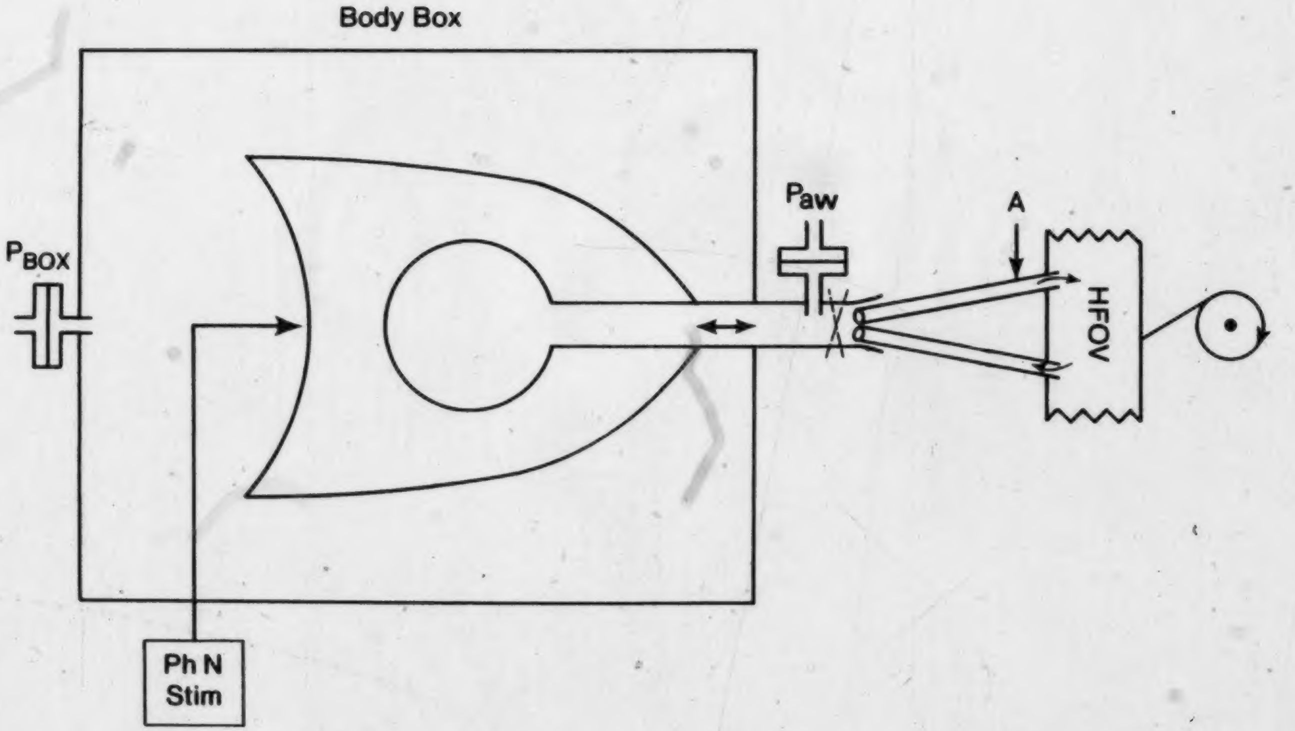
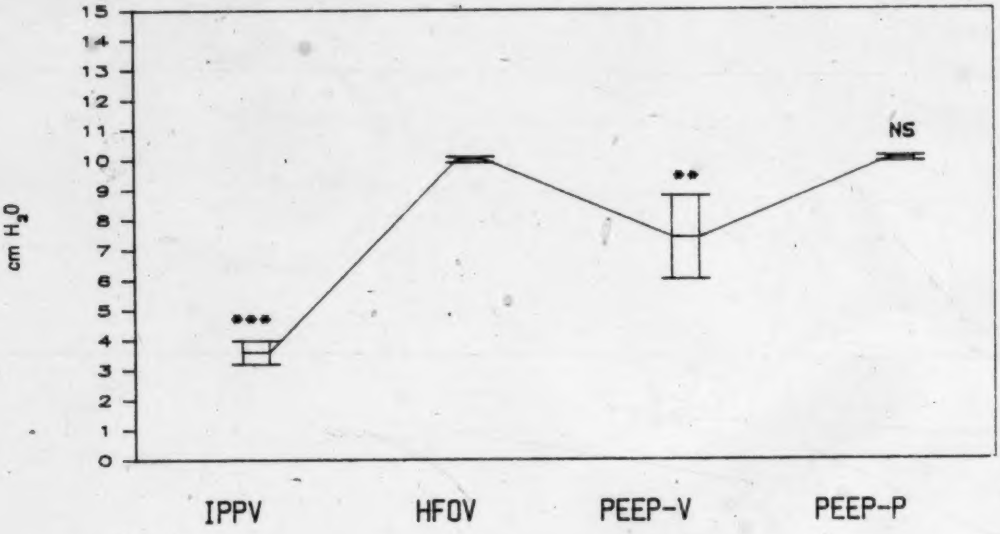

Body Box
P_{BOX}
P_{aw}
A
HFOV
Ph N
Stim

Figure 3-1: Diagram of the HFOV circuit-plethysmograph system. A, bias flow; Paw, airway-pressure transducer; Pbox, box-pressure transducer; PhN Stim, phrenic-nerve stimulator.

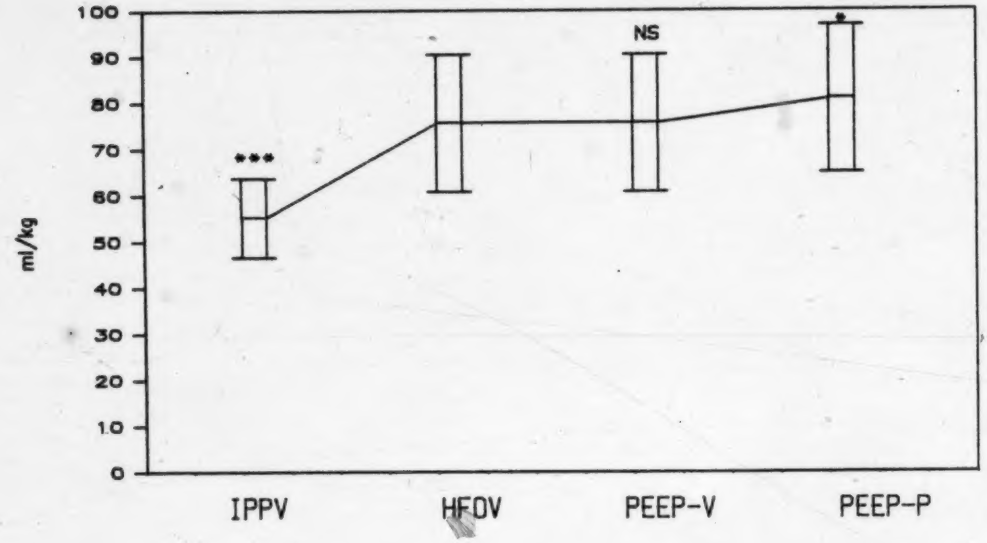
$\overline{Pd}$

Fig. 3-2



LUNG VOLUME

Fig. 3-3



Figures 3-2 and 3-3: Average of mean distal airway pressure (top) and mean lung volume (bottom) changes (±SD) during the 4 ventilatory modes. NS, $p>0.05$; *, $0.05>p>0.01$; **, $0.01>p>0.001$; ***, $p<0.001$.

Fig. 3-4

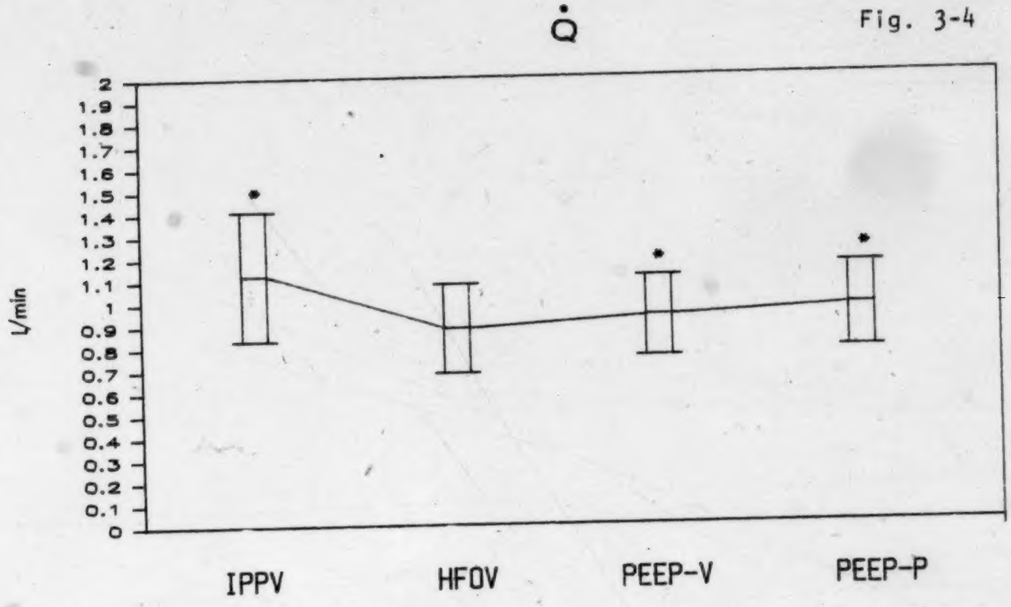
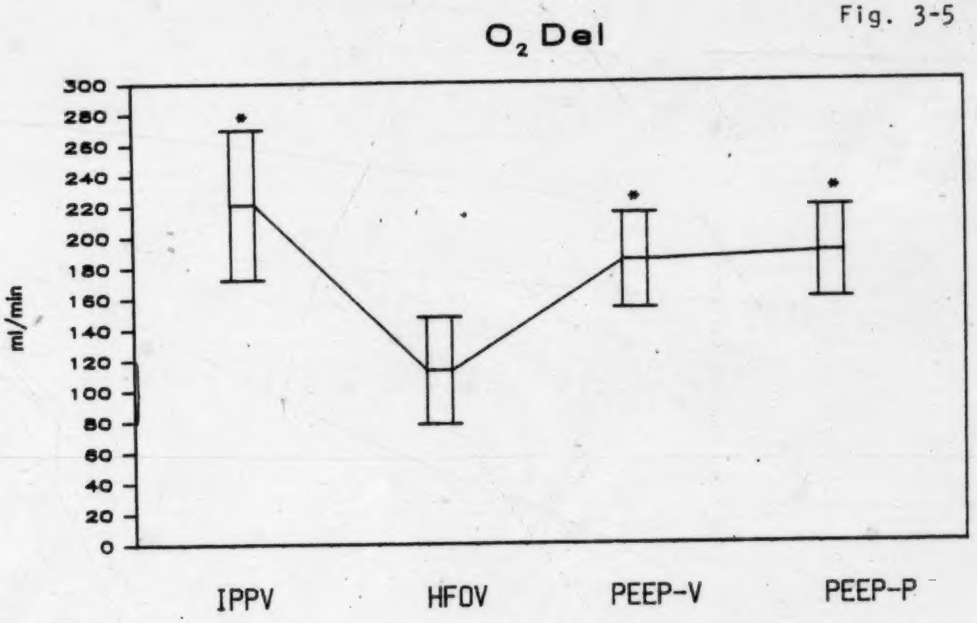


Fig. 3-5



Figures 3-4 and 3-5: Average of cardiac output (top) and oxygen delivery (bottom) changes (±SD) during the 4 ventilatory modes. Symbols as in Fig 3-2.

Fig. 3-6

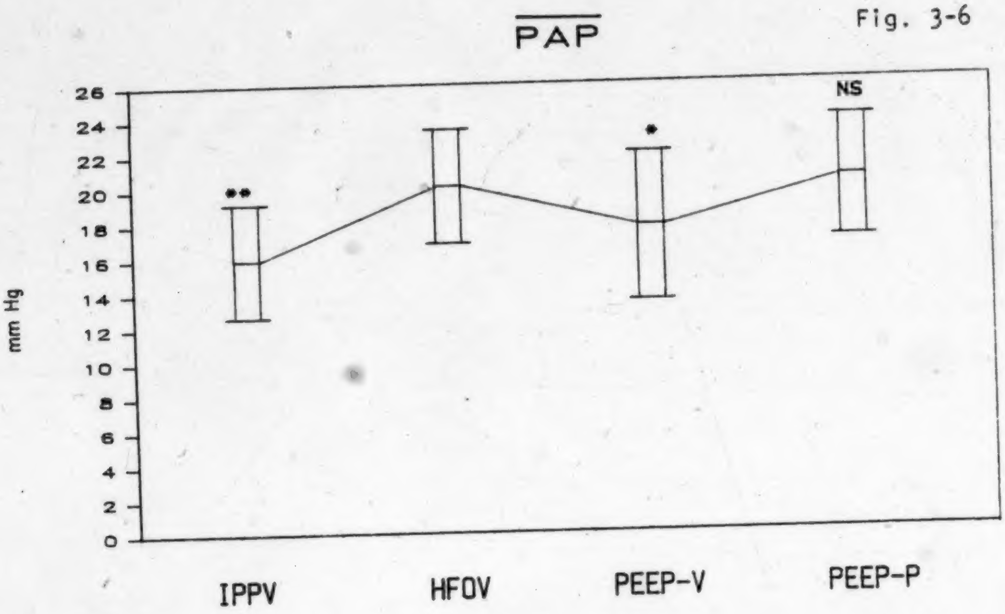
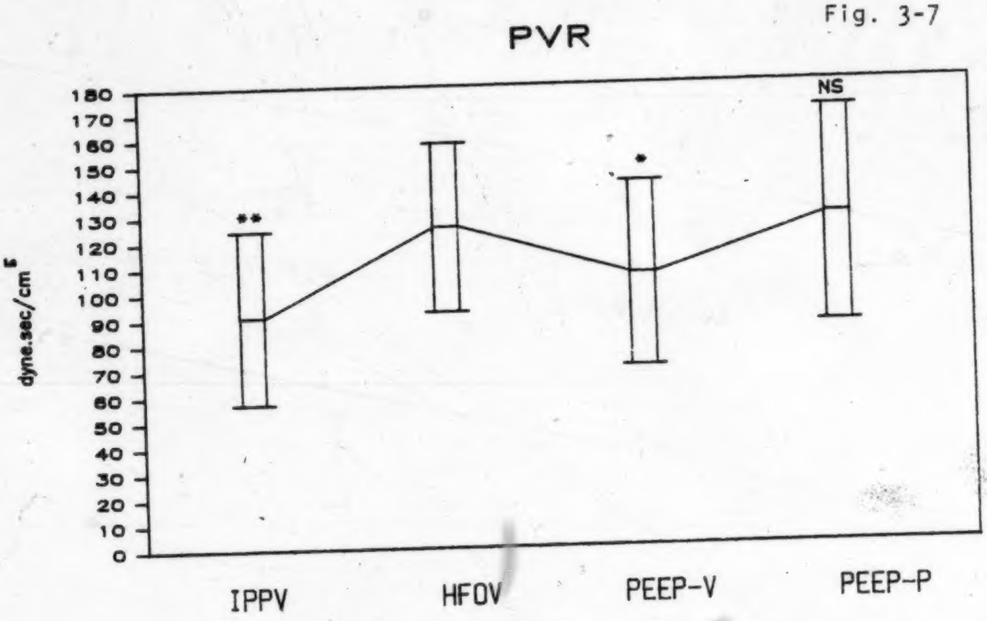


Fig. 3-7



Figures 3-6 and 3-7: Average of mean pulmonary artery pressure (top) and pulmonary vascular resistance (bottom) changes (±SD) during the 4 ventilatory modes. Symbols as in Fig 3-2.

Fig. 3-8

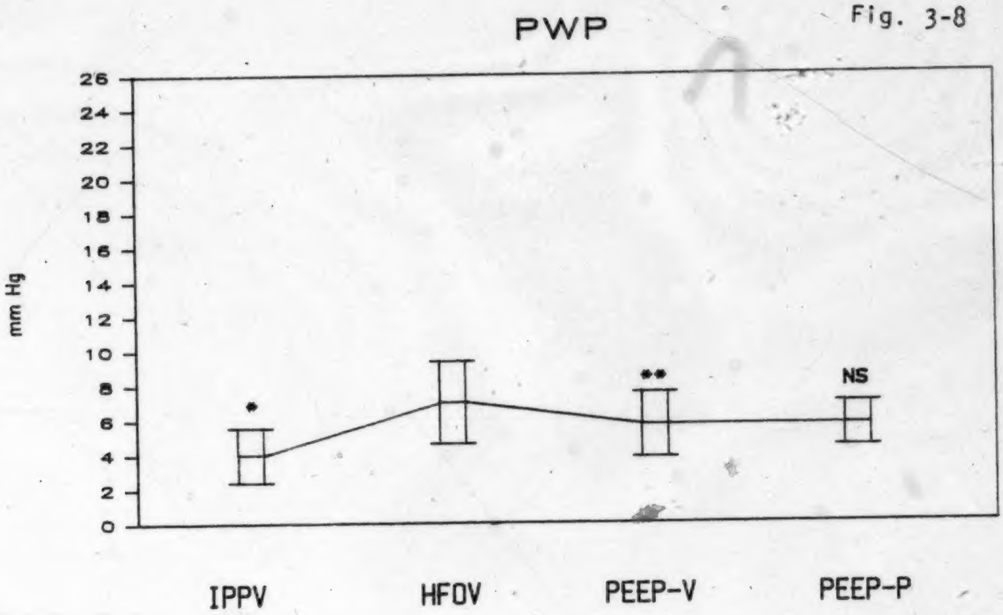
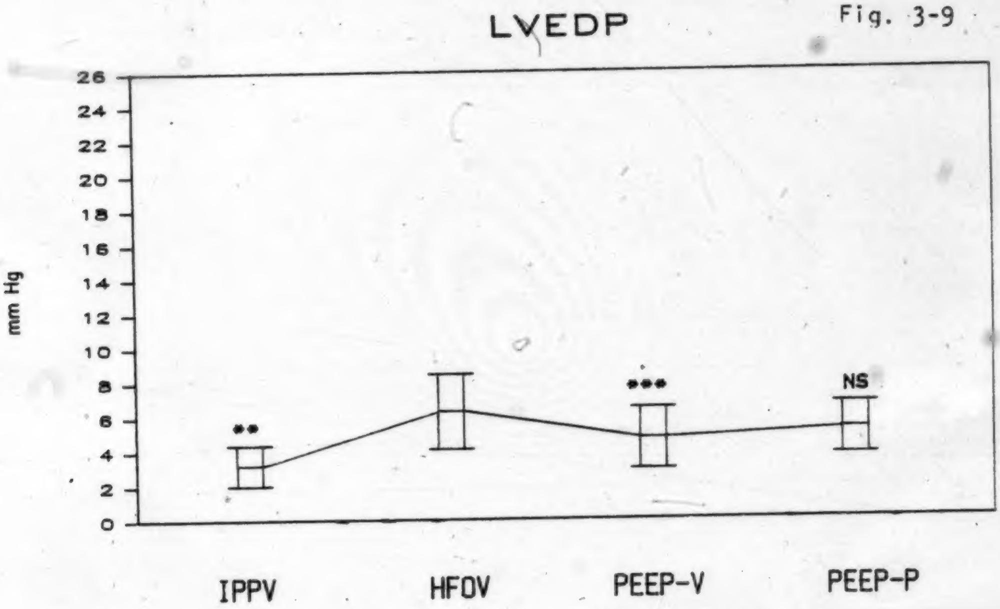


Fig. 3-9



Figures 3-8 and 3-9: Average of pulmonary wedge pressure (top) and left-ventricular end-diastolic pressure (bottom) changes (±SD) during the 4 ventilatory modes. Symbols as in Fig 3-2.

Fig. 3-10

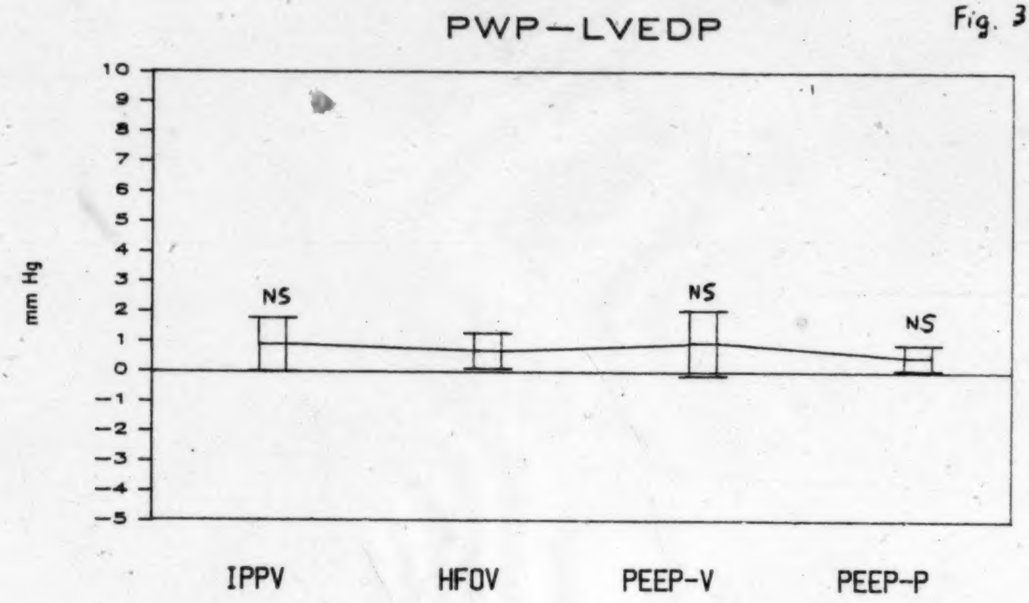
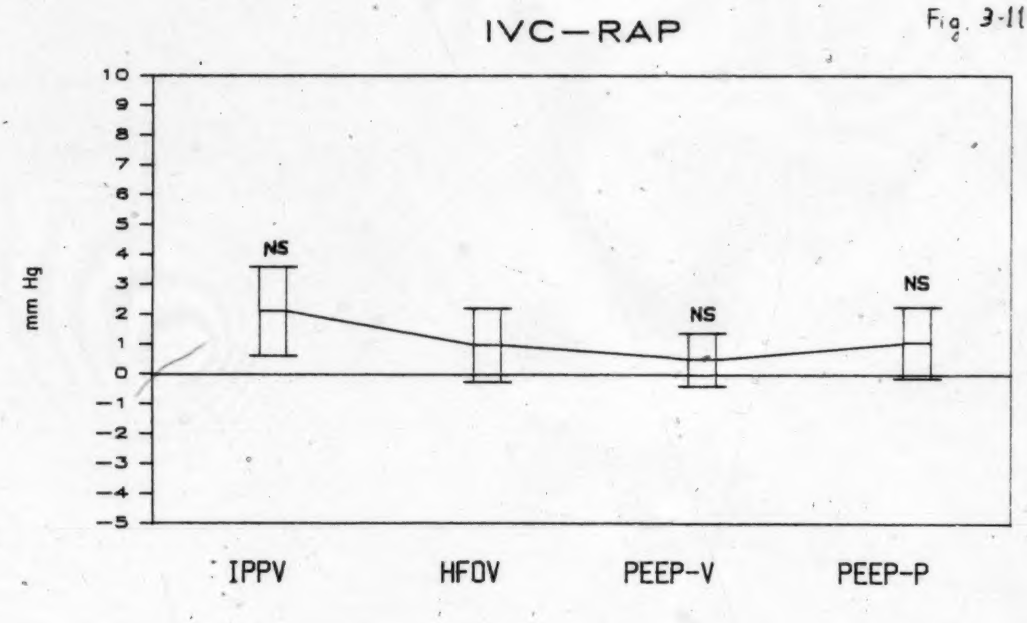


Fig. 3-11



Figures 3-10 and 3-11: Average differences, pulmonary wedge minus left-ventricular end-diastolic pressures (top) and inferior vena cava minus right atrial pressures (bottom) during the 4 ventilatory modes. Symbols as in Fig 3-2.

CHAPTER 4

HEMODYNAMIC PARAMETERS MEASURED DURING HFOV AT DIFFERENT LUNG VOLUMES AND ALVEOLAR PRESSURES

INTRODUCTION

In Chapter 1 the effects of changing HFOV frequency on cardiovascular function were examined. The results of those experiments suggested that the variations in $\overline{\text{Palv}}$ and $\overline{V}_L$ are major determinants of cardiovascular status during HFOV. In Chapter 2, it was observed that the changes in frequency are followed by variations of $\overline{\text{Palv}}$ and $\overline{V}_L$ in the same direction. The present experiments were designed to study the acute effects of changes in $\overline{\text{Palv}}$ (and $\overline{V}_L$) on cardiovascular function at a constant HFOV frequency. For this, a group of animals were ventilated at 20 Hz, and several hemodynamic parameters measured at different $\overline{\text{Palv}}$ (assessed by $\overline{\text{Pd}}$) while the changes in $\overline{V}_L$ were being monitored.

MATERIALS AND METHODS

Seven mongrel dogs (7.5 ± 0.8 kg) were anesthetized, intubated and placed in a 100-L plethysmograph box after being instrumented as described in Chapter 3. The preparation allowed the monitoring of the following lung mechanics and hemodynamics: $\overline{\text{Pd}}$, $\overline{V}_L$, IVCP, RAP, PAP, PWP, SAP, LVEDP and dP/dt. With the experimental setup it was possible to change $\overline{\text{Pd}}$ by varying the airway-chamber pressure (APC, Fig.4-1). This chamber (290 ml) enclosed the HFOV catheters and tip of the ETT. One side of the chamber was connected to a vacuum source (VS) that sucked 25 L/min continuously. The other side was attached to a positive-pressure source (HPS) with adjustable flow and to a modified PEEP chamber (M-PEEP) which could provide pressures in the system from -25 to +25 cm H_2O.

When box temperature had equilibrated (1 hour after closing the plethysmograph lid), baseline blood gases were obtained after 15—20 min of HFOV at 20 Hz, 4 L/min bias flow and a $\overline{P}d$ of 10 cm H_2O. After a few minutes of conventional ventilation (at PEEP of 4—6 cm H_2O) the ventilator was stopped and a baseline TGV was obtained by phrenic-nerve stimulation (see Appendix III), followed by a static P/V curve ($\overline{V}_L$ was monitored continuously by measuring changes in plethysmograph volume with the bell spirometer, after the TGV measurement). The animals were then connected to the HFOV circuit and the airway-chamber pressure was adjusted to induce a $\overline{P}d$ of approximately 16 cm H_2O. After 3—5 min, readings for hemodynamic parameters were taken and then $\overline{P}d$ was decreased by several cm H_2O. More hemodynamic readings were taken after a similar waiting period, and the process repeated once more at a lower $\overline{P}d$. The HFOV circuit was then disconnected and conventional ventilation restarted (at PEEP 4—6 cm H_2O) for 10—15 min. Another baseline TGV measurement was then made and three more sets of hemodynamic parameters measured during HFOV as before, at three different $\overline{P}d$ levels. In preliminary trials it was found that $\overline{PAP}$ was a good indicator of oxygenation and ventilation: whenever an HFOV setting induced poor gas exchange, $\overline{PAP}$ raised progressively and did not follow $\overline{V}_L$ changes (as it did during optimal conditions). Whenever a $\overline{P}d$ level (always in the low range) induced a steady increase in $\overline{PAP}$, no measurements were taken and $\overline{P}d$ was raised a few cm H_2O until $\overline{PAP}$ was stable. $\overline{V}_L$ was obtained by adding lung volume changes (obtained from the tracings of the output of the spirometer's linear-displacement transducer) to baseline TGV. Six sets of hemodynamic parameters were obtained, together with coresopnding $\overline{V}_L$ and $\overline{P}d$ values.

At the end of the experiments a static P/V curve of the respiratory system was obtained, using the technique described in Chapter 2. The four lower P/V points of the deflation limb were fitted into a linear regression equation (least squares method, Ref.1) and Cst obtained from the slope of the line. "Compliance" during HFOV was obtained from the slope of the correlation line $\overline{V}_L/\overline{P}d$.

Statistical analysis: Linear correlation of the hemodynamic parameters with $\overline{V}_L$ and $\overline{P}d$ was assessed by the least squares method (1). A paired t-test analysis was used to compare Cst with HFOV "compliance". Correlation between some pairs of hemodynamic parameters was also tested. To correct for simultaneous dependence on lung volume changes, a partial correlation analysis (2) was applied. Significance of the t value and correlation coefficients was established at $p<0.05$.

RESULTS

Baseline blood gases (mean ± SD) were: $PaO_2 = 96.9 \pm 5.5$ torr; a pH 7.36 ± 0.02; $PaCO_2 = 29.8 \pm 2.4$ torr. Baseline FRC was 49.7 ± 8.9 ml/kg. Table 4-1 shows the linear correlation coefficients (and significance levels) of the hemodynamic parameters with $\overline{V}_L$ (A) and $\overline{P}d$ (B). All dogs showed a high correlation between $\overline{P}d$ and $\overline{V}_L$ (Table 4-2 and Fig.4-2), and all but two hemodynamic parameters ($\overline{SAP}$ and dP/dt) showed a good correlation with both $\overline{P}d$ and $\overline{V}_L$. $\overline{PAP}$ was slightly better correlated with $\overline{V}_L$ (Figs.4-3 and 4-4) and PWP had similar correlations with both $\overline{V}_L$ and $\overline{P}d$ (Figs.4-5 and 4-6); RAP (Table 4-1), LVEDP (Figs.4-7 and 4-8) and IVCP (Table 4-1) had less consistent correlations. All parameters that showed signficant correlation with $\overline{V}_L$ or $\overline{P}d$, had a positive slope i.e.: values increased as $\overline{V}_L$ or $\overline{P}d$ increased; in those few cases where the slope was negative the correlation was not significant. Table 4-3 shows the correlation analyses of pairs of parameters. PWP showed a good correlation with LVEDP and $\overline{PAP}$, also RAP was correlated with IVCP; dP/dt was not correlated with either LVEDP or $\overline{SAP}$. The partial correlation analysis showed that the interrelation between PWP and $\overline{PAP}$ was due mainly to the influence of lung volume; the correlations between PWP and LVEDP and between RAP and IVCP were only partially influenced by lung volume effects; the correlation between dP/dt and $\overline{SAP}$ was only apparent when the lung volume factor was removed (Table 4-3, values in parenthesis). Cst values in 5 of the 7 dogs were slightly higher than HFOV "compliance", but the overall differences were not signficant (Table 4-2); in all cases the correlation between $\bar{P}d$ and $\bar{V}_L$ was linear ($p<0.01$).

DISCUSSION

The present experiments demonstrate the importance of lung volume and $\bar{P}alv$ on the cardiovascular changes induced by HFOV. The major effects of $\bar{V}_L$ and $\bar{P}d$ were on the pulmonary circulation and systemic venous return. There was a very strong correlation between $\bar{P}d$ and $\bar{V}_L$ (Table 4-2) which intefered with the analysis of separating the individual effects of pressure and volume on the hemodynamic parameters. During static conditions there was a tendency (not significant) for slightly higher respiratory system compliance than during HFOV. This finding agrees with the data from Chapter 6, which suggested that during HFOV the lung is situated halfway between the inflation and deflation limbs of the static P/V curve of the respiratory system.

$\bar{P}d$ was used as an estimate of $\bar{P}alv$ because proximal $\bar{P}aw$ underestimates respiratory zone pressure (Chapter 9A). Results from other experiments (Chapter 6) suggested that $\overline{P}d$ is a satisfactory estimate of $\overline{P}alv$. The range of $\overline{P}d$ tested was determined by the characteristics of the present experimental preparation: the lower limit was the minimum pressure required for satisfactory gas exchange; the upper limit was somewhat arbitrarily set to avoid major cardiovascular depression (that could cause the preparation to deteriorate) and also to prevent barotrauma. The strict control of volume changes did not permit an extension of the test periods to include $\dot{Q}$ and blood gas measurements. Minor changes in PaO_2 or $PaCO_2$ could therefore have been present but major fluctuations that might have significant cardiovascular effects were avoided by rejecting measurements at $\overline{P}d$ levels that induced a steady increase in $\overline{PAP}$ (this was a rare occurrence at $\overline{P}d>6$ cm H_2O). In Chapter 2 it was found that the changes in $\overline{V}_L$ induced by HFOV are established in less than 1 min, consequently the 3-5 min waiting period of the present experiments would be sufficient to achieve steady state conditions. The different $\overline{P}d$ levels were tested in groups of 3 and starting by the high ones, to prevent accumulative effects of potential poor gas exchange conditions induced by low $\overline{P}d$, and avoid large fluctuations in cardiovascular status that would require long periods of equilibration. The tracings obtained in the present experiments suggested that the hemodynamic parameters were in a steady state when measured, however additional changes induced by longer periods of HFOV cannot be excluded.

The observed increase in $\overline{PAP}$ was probably due to the compression of the capillaries by high $\overline{P}alv$ and the stretching of the pulmonary vessels induced by high lung volumes (3). The results of Chapter 9C exclude a role for PG's in this response. The correlation analyses suggest that

$\overline{PAP}$ was more related to $\overline{V}_L$ than to $\overline{P}d$ (Table 4-1), however, the strong P/V correlation observed impeded the separation of these two effects. PWP was usually correlated with LVEDP, even after removing the influence of $\overline{V}_L$ (Table 4-2). The changes in PWP and LVEDP were probably induced mostly by intrapulmonary pressure fluctuations. The lack of correlation between dP/dt and LVEDP suggests that LV function changes were not related to fluctuations in preload; the correlation between dP/dt and $\overline{SAP}$ after removing the effect of $\overline{V}_L$ suggests that afterload modified LV function, and that $\overline{V}_L$ had opposite effects on dP/dt and $\overline{SAP}$. In Chapters 1 and 3 it was found that HFOV decreased $\dot{Q}$, thus the increases in IVCP and RAP observed in the present experiments are probably due to an obstruction to venous return caused by an augmented pleural pressure.

In summary, the results of the present experiments indicate that during HFOV, the changes in hemodynamic parameters (mainly $\overline{PAP}$, PWP, LVEDP and RAP) are related to increases in $\overline{V}_L$ and $\overline{P}alv$. The P/V characteristics of the respiratory system during HFOV are comparable to those found during static conditions without HFOV.

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2. SNEDECOR G.W., AND W.G. COCHRAN. Statistical methods, 6th ed. Ames, IO: Iowa State University Press; 1967: 400-403.

3. WHITTENBERGER J.L., M. MCGREGOR, E. BERGLUND, AND H.G. BORST. Influence of state of inflation of the lung on pulmonary vascular resistance. J. Appl. Physiol. 15: 878-882, 1960.759,and745

TABLE 4-1: Linear correlation coefficients of hemodynamic parameters:

A) With mean lung volume

Dog#	$\overline{\text{PAP}}$	PWP	LVEDP	dP/dt	$\overline{\text{SAP}}$	RAP	IVC
1	0.85	0.97	0.34	0.01	0.19	0.01	0.05
	*	**	NS	NS	NS	NS	NS
2	0.94	0.95	0.87	0.30	0.19	0.13	0.35
	**	**	*	NS	NS	NS	NS
3	0.92	0.87	0.87	0.56	0.91	0.90	0.97
	*	*	*	NS	*	*	**
4	0.88	0.86	0.70	0.04	0.46	0.99	0.90
	*	*	NS	NS	NS	***	*
5	0.92	0.88	0.86	0.04	0.64	0.96	0.68
	**	*	*	NS	NS	**	NS
6	0.94	0.98	0.93	0.79	0.38	0.83	0.78
	**	***	**	*	NS	*	*
7	0.90	0.81	0.59	0.53	0.06	0.87	0.92
	*	*	NS	NS	NS	*	**
B) With mean distal airway pressure							
1	0.91	0.99	0.51	0.16	0.06	0.10	0.10
	*	***	NS	NS	NS	NS	NS
2	0.91	0.91	0.82	0.24	0.098	0.23	0.41
	*	*	*	NS	NS	NS	NS
3	0.97	0.83	0.81	0.64	0.86	0.93	0.99
	**	*	NS	NS	*	**	***
4	0.91	0.91	0.51	0.35	0.56	0.94	0.852
	*	*	NS	NS	NS	**	*
5	0.81	0.96	0.91	0.17	0.42	0.88	0.81
	NS	**	*	NS	NS	*	NS
6	0.93	0.99	0.93	0.83	0.30	0.84	0.80
	**	***	**	*	NS	*	*
7	0.89	0.87	0.67	0.55	0.03	0.82	0.98
	*	*	NS	NS	NS	*	***

Symbols: NS, $p>0.05$; *; $0.05>p>0.01$; **; $0.01>p>0.001$; ***; $p<0.001$.

TABLE 4-2: HFOV "Compliance" and deflation Cst, in ml/cm H_2O

Dog#	1	2	3	4	5	6	7	Mean ± SD
HFOV (r value)	21.3 (0.96)	14.9 (0.99)	11.0 (0.98)	17.6 (0.94)	15.2 (0.94)	12.1 (0.99)	16.3 (0.98)	15.4 ±3.45
Static (r value)	19.6 (0.99)	24.2 (0.99)	14.7 (0.99)	20.1 (0.99)	20.9 (0.99)	14.0 (0.99)	13.7 (0.99)	18.2 ±4.05

Significance of the correlation coefficients: $p<0.01$. Paired t-test, $t = 1.370$; $p>0.05$

TABLE 4-3: Linear correlation coefficients of pairs of hemodynamic parameters

Dog #	PWP/LVEDP	PWP/$\overline{PAP}$	IVCP/RAP	dP-dt/LVEDP	dP-dt/$\overline{SAP}$
1	0.43(0.44) NS (NS)	0.86(0.28) * (NS)	0.78(0.78) * (*)	0.09(0.09) NS (NS)	0.68(0.69) NS (NS)
2	0.97(0.91) ***(**)	0.96(0.62) ***(NS)	0.84(0.85) * (*)	0.58(0.67) NS (NS)	0.79(0.79) * (*)
3	0.98(92) ***(**)	0.75(0.30) NS (NS)	0.94(0.66) ** (NS)	0.18(0.74) NS (NS)	0.19(0.91) NS (**)
4	0.48(0.40) NS (NS)	0.83(0.25) * (NS)	0.93(0.51) ** (NS)	0.22(0.27) NS (NS)	0.68(0.74) NS (NS)
5	0.83(0.30) * (NS)	0.73(0.47) NS (NS)	0.56(0.44) NS (NS)	0.05(0.03) NS (NS)	0.69(0.86) NS (*)
6	0.98(0.21) ** (NS)	0.89(0.45) ** (NS)	0.93(0.81) ** (*)	0.79(0.25) * (NS)	0.26(0.07) NS (NS)
7	0.57(0.19) NS (NS)	0.88(0.61) ** (NS)	0.78(0.13) * (NS)	0.14(0.26) NS (NS)	0.73(0.82) NS (*)

Symbols as in Table 4-1. Data in parenthesis are correlation coefficients corrected for lung volume changes

Fig. 4-1

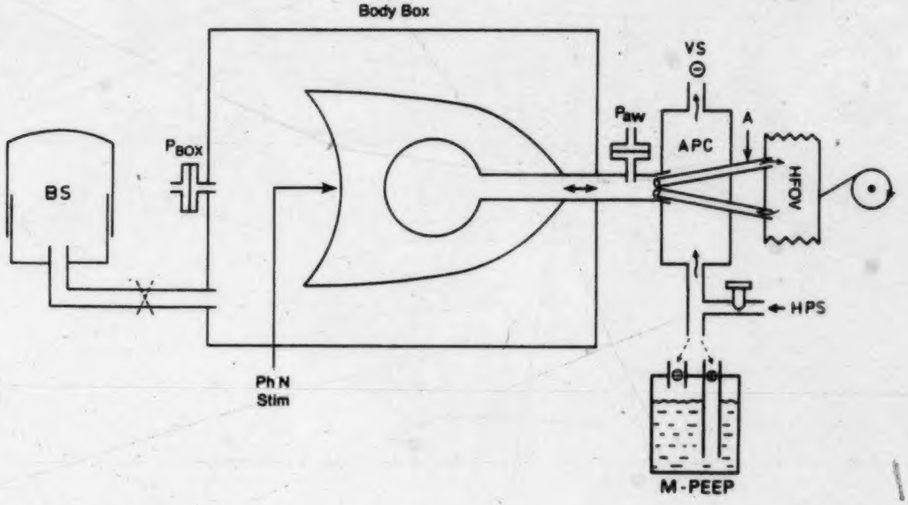

Body Box
VS
P_{aw}
APC
A
HFOV
P_{BOX}
BS
PhN Stim
HPS
M-PEEP

Fig. 4-2

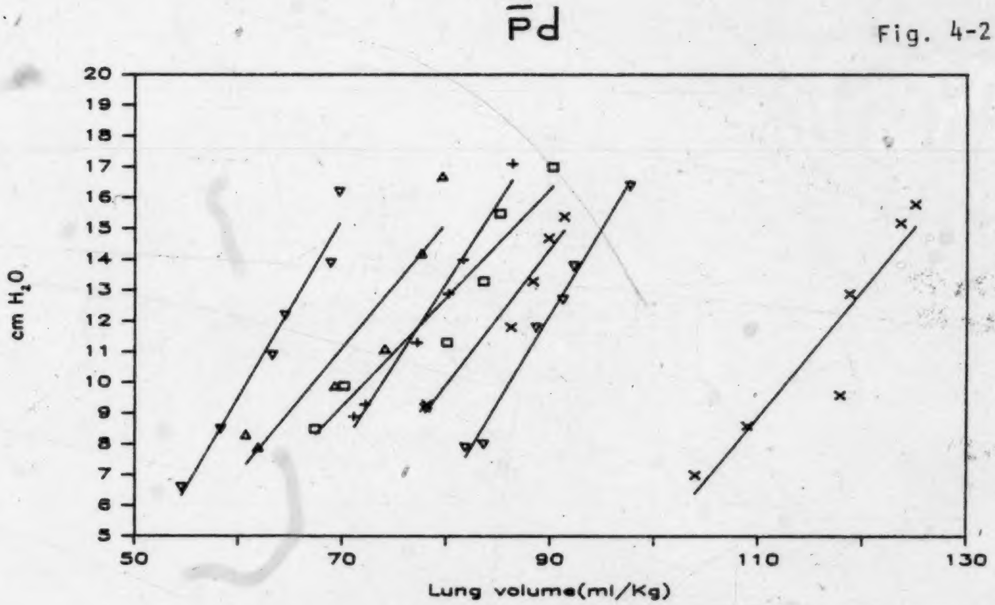
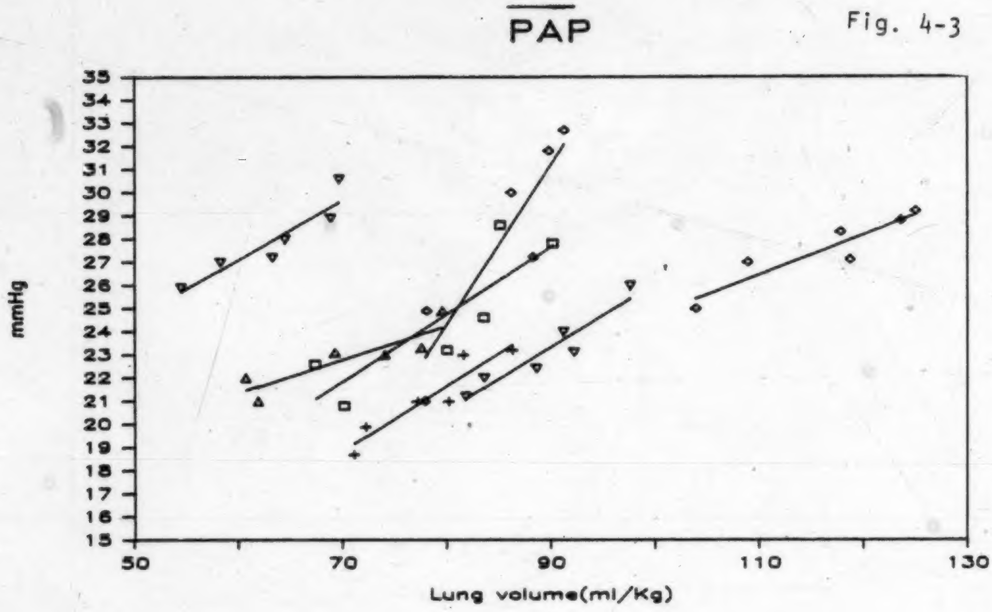
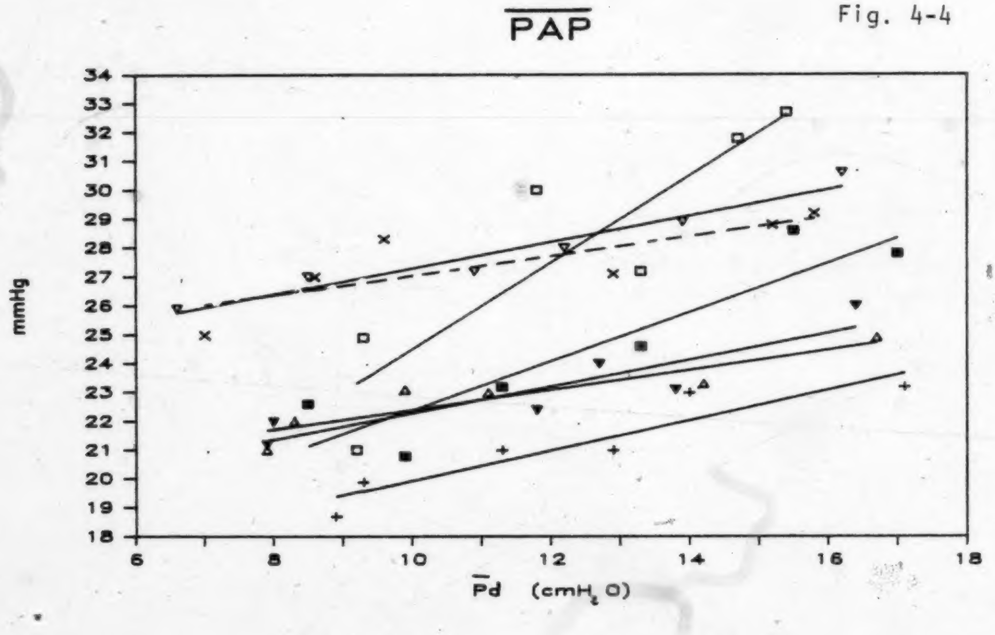
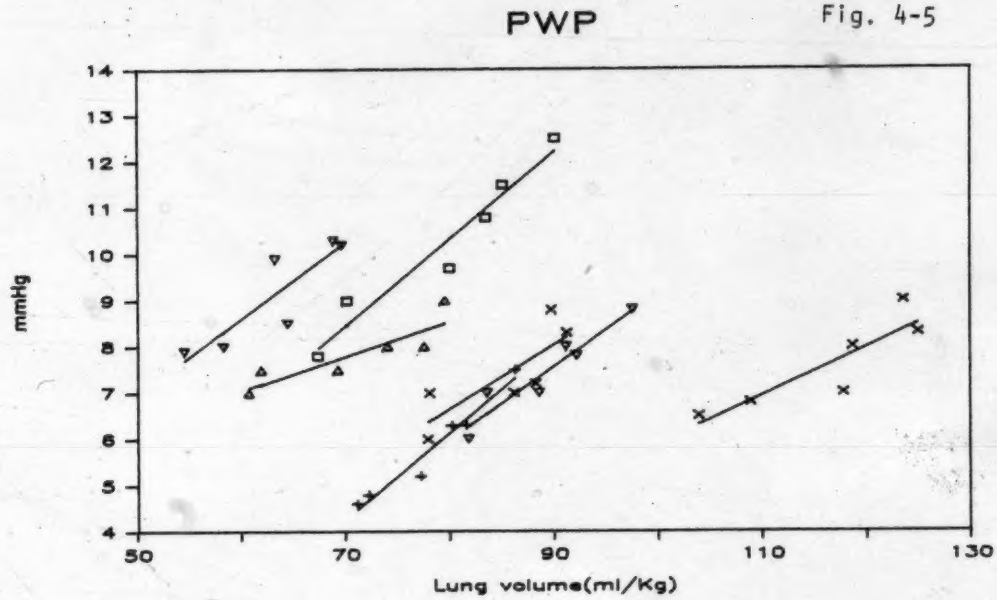


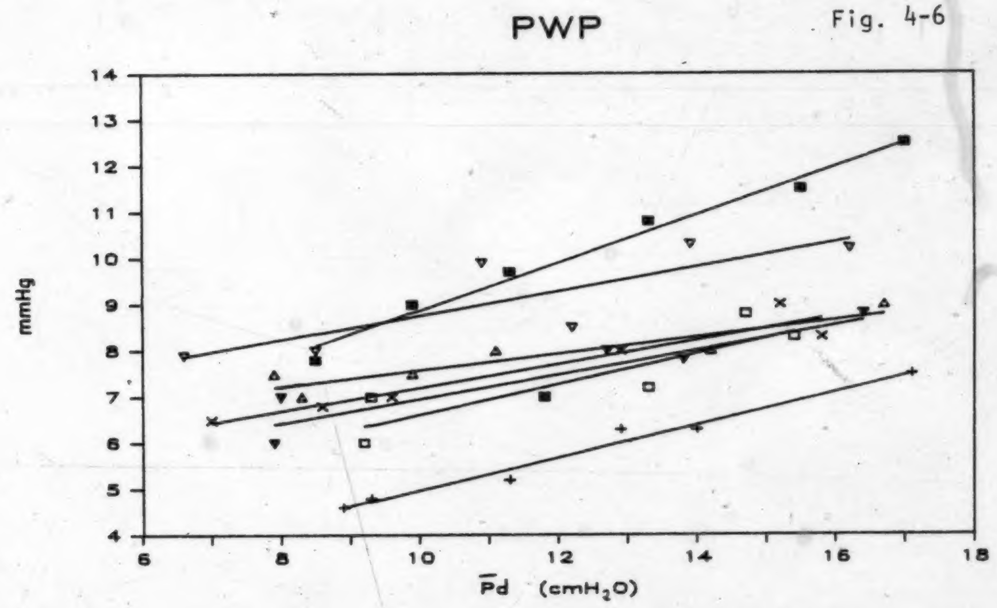
Figure 4-1: Diagram of the HFOV circuit and plethysmograph. A, bias flow; APC, airway pressure chamber; BS, bell spirometer; HPS, high pressure source; M-PEEP, modified PEEP chamber; Paw, airway pressure transducer; P_{BOX}, box pressure transducer; PhN, phrenic-nerve stimulator; VS, vacuum source. Figure 4-2: Changes in airway pressure with lung volume, showing linear regression lines for individual dogs.





Figures 4-3 and 4-4: Changes in mean pulmonary artery pressure with lung volume (top) and mean distal airway pressure (bottom) showing regression lines for individual dogs. Dashed line, correlation not significant.





Figures 4-5 and 4-6: Changes in mean pulmonary wedge pressure with lung volume (top) and mean distal airway pressure (bottom) showing regression lines for individual dogs.

Fig. 4-7

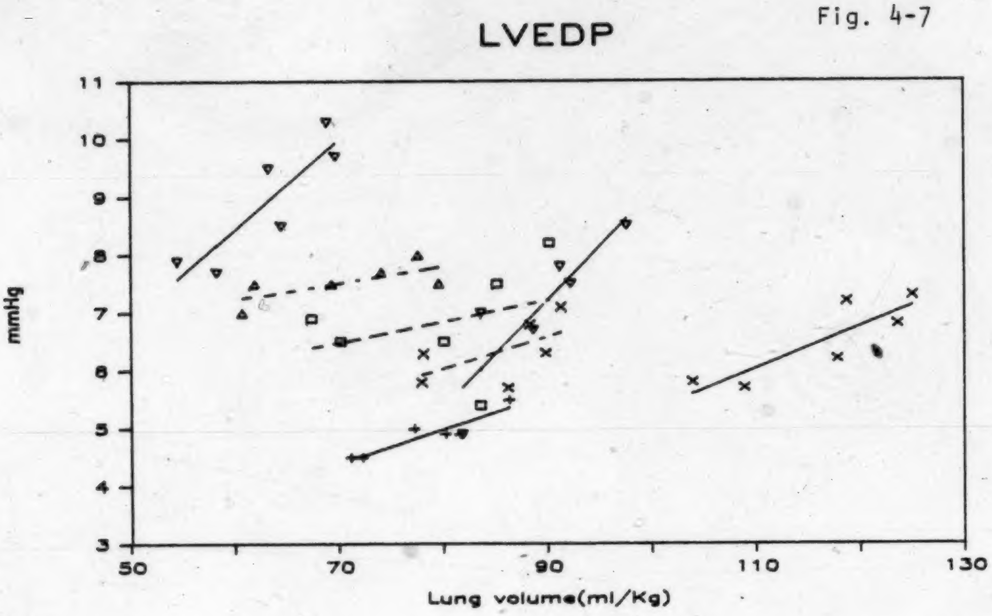
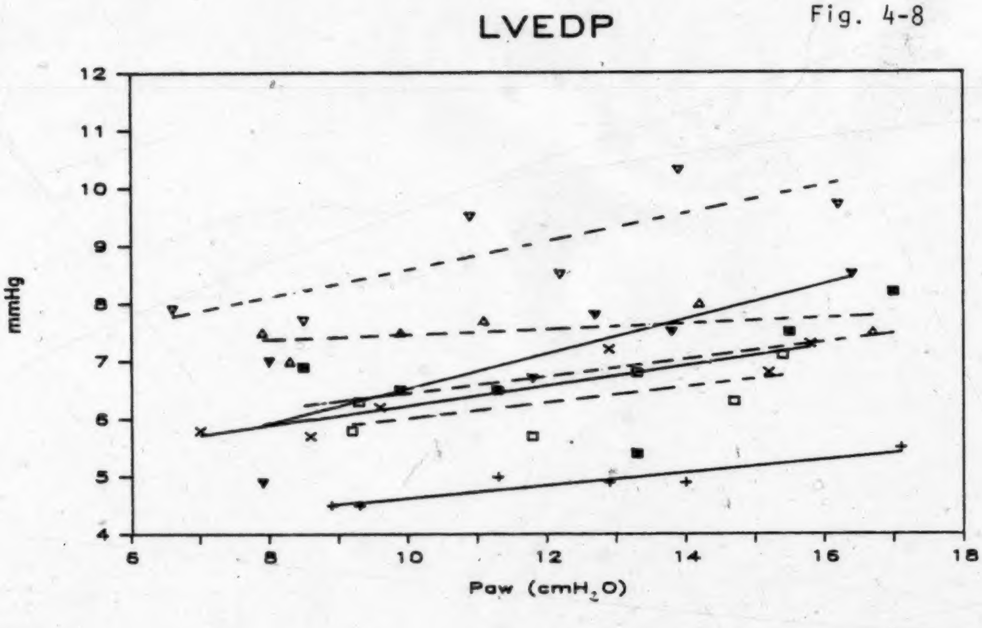


Fig. 4-8



Figures 4-7 and 4-8: Changes in left-ventricular end-diastolic pressure with lung volume (top) and mean distal airway pressure (bottom) showing regression lines for individual dogs. Dashed line, correlation not significant.

CHAPTER 5

EFFECTS OF HFOV AND PEEP AT CONSTANT $\overline{P}aw$ ON DOGS WITH LOW-COMPLIANCE LUNGS

INTRODUCTION

Appendix IV describes a method for decreasing the compliance of dog lungs. The stiff lungs were produced by repeated washings with warm saline, which probably depleted the alveoli and airways of surface-active material. After the lungs became stiff $P(A-a)O_2$ increased but hemodynamics were almost unaffected. After a period of "stabilization" (1 h on IPPV) the pathophysiologic changes became stable for at least 4 h. Thus, this type of lung damage affects mechanical and gas-exchange functions primarily, with little interference with the circulation. This type of lung lesion has many similarities with two common clinical syndromes: IRDS (2) and ARDS (4). The effects of HFOV on the saline lavaged lungs could provide information useful for understanding the role of HFOV in clinical practice.

In this chapter, the effects of HFOV are compared to PEEP (at similar $\bar{P}aw$), in eight pentobarbital-anesthetized dogs with saline-induced lung damage.

METHODS

Eight dogs (8.3 ± 1.8 kg) were used for the experiments. After being anesthetized, they were intubated and instrumented as described in the previous chapter. In addition, the phrenic nerves were isolated and connected to a physiologic stimulator, and the animals placed in a body plethysmograph to measure TGV as described in Appendix III. The animals were ventilated with a Harvard respirator (model 607) at 15 bpm and V_T of 15 ml/kg (and 3 cm H_2O PEEP during the preparation period). After preparation had been completed, the animals were placed in the plethysmograph and V_T adjusted to induce a $PaCO_2$ of 30 ± 2 mmHg (at zero

PEEP); the dogs were subsequently ventilated with 3 cm H_2O of PEEP. When the animals had been in the plethysmograph for 1 h, PEEP was set at zero and 20 min later baseline measurements were taken. The parameters measured (obtained as described in Appendix VI) were: Cst, $\overline{P}$aw, $\overline{P}$eso, $\overline{P}_L$, PaO_2, $P(A-a)O_2$, $PaCO_2$, $\overline{PAP}$, PWP, LVEDP, LVSP and dP/dt; also, TGV and $\overline{V}_L$ were calculated as described in Chapter 4. After making the measurements, the animals were ventilated with the Harvard respirator with 100% O_2 and 3 cm H_2O PEEP; 20 min later saline lavage of the lungs was performed as described in the previous chapter. After the lavage, the animals were ventilated with IPPV (and 100% O_2) for 60 min and all the measurements repeated.

The animals were assigned at random (restricted randomization) to two groups: HFOV and PEEP. The 4 animals in the HFOV group were first ventilated with 3 cm H_2O PEEP for 10 min and the $\overline{P}$aw reading noted; the dogs were then ventilated with the HFOV circuit described in Chapter 4, at 20 Hz and 24 L/min of O_2 (bias flow). The pressure in the airway chamber was adjusted to induce the same $\overline{P}$aw than during PEEP ventilation. During the first few minutes of HFOV, several sigh maneuvers were performed by raising the pressure in the airway chamber for 4--6 s, inducing a $\overline{P}$aw of around 25 cm H_2O. After 30 min of HFOV, all the measurements were repeated, and the animals ventilated with the Harvard respirator with 3 cm H_2O PEEP and 100% O_2. Thirty minutes later, another set of measurements was taken. The HFOV and PEEP studies were done again, with corresponding measurements repeated. During PEEP the sigh maneuvers were performed with a volume equal to twice V_T by clamping the expiratory line. In some cases, after lavage, the animals attempted to breathe spontaneously during IPPV (while anesthetized), probably due to hypercapnia. In these situations the respirator rate was increased to 22--24 bpm to maintain apnea.

The animals in the PEEP group were first ventilated with 3 cm H_2O PEEP for 40 min (10 + 30 min) and measurements were taken. Three more sets of measurements were obtained after placing the animals on HFOV for 30 min (at the same $\overline{P}aw$ level induced by PEEP), PEEP and again HFOV.

The TGV measurements were performed after opening the airway to atmospheric pressure for 6--8 s. To obtain $\bar{V}_L$ during HFOV, the volume expired (measured with the spirometer) when HFOV was disconnected, was added to the previously-measured TGV. $\bar{V}_L$ during IPPV was obtained by adding to TGV the average volume changes induced by V_T (from the spirometer tracings; see Chapter 3). To calculate $\bar{V}_L$ during PEEP, the volume expired when PEEP was disconnected at end-expiration (measured with the spirometer) was added to the average of the lung volume changes induced by V_T (between end-expiration and end-inspiration), and to measured TGV.

Statistical analysis: To test for overall differences between PEEP and HFOV periods (post-lavage) a 2-way ANOVA (6) was used. Individual differences between HFOV and PEEP during the first or second periods were tested with Duncan's multiple-range test (1). Pre-lavage baseline and post-lavage IPPV measurements were not included in the statistical analysis. Values are presented as means ± SD; significance value was set at $p<0.05$.

RESULTS

Table 5-1 shows the average values of each parameter, obtained during the pre-lavage control period, post-lavage IPPV and the two HFOV and PEEP periods; statistical analysis (ANOVA and Duncan tests) is also included. As expected, Cst decreased after lavage (Fig.5-1) and this was accompanied by an increase in $\overline{P}$aw (Fig.5-2) and $\overline{P}_L$(Fig.5-3); Peso decreased concomitantly (Fig.5-4). Cst and $\overline{P}$aw were similar during HFOV and PEEP, but$\overline{P}$eso was lower and $\overline{P}_L$ higher during HFOV. TGV decreased after lavage and remained similar during HFOV and PEEPFig.5-5); $\overline{V}_L$ also decreased after lavage, and was significantly higher during HFOV (Fig.5-6). PaO_2 was significantly higher during HFOV (Fig.5-7) and $P(A-a)O_2$ was significantly lower; $PaCO_2$ was slightly higher during HFOV (Fig.5-8) but the differences were not significant. $\overline{PAP}$ increased after the lavage and was significantly higher during HFOV (Fig.5-9); the same was true for PWP (Fig.5-10) and LVEDP. Both LVSP and dP/dt decreased somewhat after lavage, and there were no significant differences between HFOV and PEEP.

When the first and second test periods were compared statistically (Duncan's test), no significant differences were observed in any parameter between the two HFOV periods, or between the two PEEP periods.

DISCUSSION

The aim of the present experiments was to compare the effects of HFOV to those of conventional ventilation in dogs with stiff lungs. In Appendix IV it is demonstrated that saline lavage induces an increase in lung stiffness which was stable for at least 4 h; the associated physiologic changes have also been described. In the present Chapter, the statistical analysis of the results was designed to compare HFOV with PEEP; the effects of lavage, although not tested statistically, seemed similar to what has been described in Appendix IV. The overall testing time was around 3 $^1/_2$h after the post-lavage IPPV period. Any changes in the stability of the lung lesion with time, would have little effect on the results because the testing periods were randomized and repeated twice. The statistical analysis did not show any significant differences between the two HFOV or PEEP periods, indicating that the degree of lung damage was quite stable during the time tested. In Appendix IV a small increase in $\overline{\text{PAP}}$ was observed at the end of the testing period; in the present experiments, an even smaller increase was found (less than 1.5 mmHg), which was not statistically significant.

For data analysis, measurements obtained during the first or second testing periods were pooled, although half of the time PEEP was tested first, and in the other half HFOV was first. This was justified because the lung injury was stable, and it would avoid any biases induced by starting the tests with a particular ventilatory mode.

In the present experiments, $\bar{P}$aw was measured at the ETT level, a location that was later found to underestimate $\bar{P}$alv by an average of around 2.2 cm H_2O (see Chapter 9A). This means that during HFOV the dogs were probably ventilated at a slightly higher $\bar{P}$alv than during PEEP. This may explain, at least in part, the higher PaO_2 and $\dot{V}_L$ during HFOV; the slightly higher $PaCO_2$ during HFOV could be due in part to larger "dead space" induced by higher small-airway distending pressures. An estimate of the $\dot{V}_L$ that would be induced by HFOV at the same $\bar{P}$alv as during PEEP, was obtained by multiplying "Cst" during HFOV by the previously-mentioned pressure gradient $\bar{P}$alv - $\bar{P}$aw (2.2 cm H_2O), and subtracting this value from $\dot{V}_L$ obtained during HFOV. $\dot{V}_L$ was an average 29% (1st period) and 27% (2nd period) higher during HFOV with no correction for $\bar{P}$alv; when adjusted for $\bar{P}$alv the differences were still important, 11% and 10% respectively. Although these calculations are only a rough estimate — which involves several assumptions and use data obtained from different experiments — they suggest that in the surfactant-deficient lung HFOV induces higher $\bar{V}_L$ than conventional ventilation at similar distending pressure. This agrees with data published by other groups who lavaged rabbits lungs (3). The results of the experiments of Chapter 3 suggest that in normal lungs conventional ventilation induces higher $\bar{V}_L$ than HFOV at the same alveolar distending pressure. This discrepancy could mean that when there is a tendency for alveolar collapse, HFOV is more efficient in maintaining alveoli in an opened state, as suggested in the previously-mentioned report (3). It is unlikely that the different techniques used for the sigh maneuvers were responsible for the observed discrepancies. In Chapter 9A, the $\bar{P}$aw gradients during HFOV were studied at a bias flow of 4 L/min, but in the present experiments the flow used was 24 L/min, which could induce a different gradient. To test this hypothesis, the gradients of two dogs were studied at a flow of 32 L/min (the maximal that could be generated in the experimental setup). The pressure differences between the ETT and distal airway were respectively 2.7 and 2.1 cm H_2O, which are in the range found in Chapter 9A using only 4 L/min of bias flow. Interestingly, in the tests with high flow, a region of low pressure was consistently identified just distal to the tip of the ETT which was 1.9 and 1.5 cm H_2O lower than average ETT readings. This effect disappeared a few centimeters distally, and the pressure increased as described previously. These findings might be explained by the turbulence created at the tip of the ETT by high gas flows. The presence of this low-pressure zone has to be considered whenever $\bar{P}$aw is measured near the tip of the ETT and high bias flows are used.

In preliminary trials it was found that the bias flow of 4 L/min used in most experiments was associated with CO_2 retention after saline lavage. An increase in bias flow to 24 L/min induced satisfactory $PaCO_2$ levels in most cases. This finding corroborates reports from other authors who have suggested that an increase in bias flow improves CO_2 removal (5,7). However, in some cases a tendency for CO_2 retention was observed during HFOV at high flows, but it was not statistically significant.

During conventional ventilation with PEEP, 100% O_2 was used, but during HFOV this was probably not the case. During HFOV, pure O_2 was used for the bias flow, but air circulated through the airway pressure chamber. The in vitro tests reported in Appendix I suggest that significant entrainment does not take place with this HFOV system, and consequently little if any, air entered the circuit in the present experiments. However, as discussed in the Introduction, signifcant rebreathing probably takes place during HFOV, and this decreases the O_2 concentration that reaches the alveoli. This makes the increased PaO_2 observed during HFOV even more significant clinically.

The experiments reported in Appendix IV suggested that saline lavage might increase the permeability of the alveolo-capillar membrane. To avoid fluid accumulation in the air spaces, minimal i.v. fluids were administered in the present experiments (similar to what was used in the previous Chapter); for the same reason, $\dot{Q}$ measurements were not performed during the experiments. The hemodynamic data suggest that HFOV induced higher pressures in the pulmonary circulation and left atrium, but the higher $\bar{P}$alv during HFOV was probably the major factor causing this. There were no significant differences in LV function (as assessed by dP/dt), but the large SD diminishes the value of this finding. LVSP was used as an index of LV performance and peripheral circulation status, but unfortunately, diastolic systemic blood pressure and $\dot{Q}$ were not available to support the findings.

In summary, the present experiments suggest that HFOV is at least as good as (and probably better than) PEEP in maintaining $\dot{V}_L$ and PaO_2 in surfactant-deficient lungs. However, in some cases, CO_2 removal could be unsatisfactory.These findings suggest that HFOV could be useful in a clinical setting to ventilate patients with surfactant-deficient and stiff lungs. However, the potential for barotrauma induced by the sigh maneuvers would have to be investigated further before starting human experiments.

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TABLE 5-1: Overall data and statistical analysis (Multiple range test and ANOVA) of the differences between HFOV and PEEP periods

	IPPV control	IPPV post-lavage	HFOV	PEEP	HFOV	PEEP	F value (ANOVA)
Cst (ml/cm H_2O)	45.8± 11.2	36.2± 18.9	32.5± 12.2(NS)	32.3± 12.8	30.6± 12.5(NS)	30.2± 11.8	1.67 (NS)
$\bar{P}aw$ (cm H_2O)	3.85± 0.80	6.53± 1.87	8.78± 2.03(NS)	8.72± 1.97	8.78± 2.01(NS)	8.82± 2.08	3.04 (NS)
$\bar{P}eso$ (cm H_2O)	2.23± 0.77	0.24± 0.71	0.34± 0.85(**)	1.03± 0.72	0.31± 0.96(**)	1.14± 0.94	11.29 (**)
$\bar{P}_L$ (cm H_2O)	1.78± 0.87	6.32± 1.56	8.37± 1.96(**)	7.76± 1.60	8.51± 1.97(**)	7.64± 1.67	8.76 (**)
FRC (ml/kg)	56.1± 8.32	33.3± 9.62	38.5± 12.1(NS)	36.0± 12.6	36.8± 14.4(NS)	35.5± 13.4	2.05 (NS)
$\bar{V}_L$ (ml/kg)	61.4± 8.37	38.3± 9.88	61.5± 14.8(**)	47.8± 13.6	59.5± 16.3(**)	46.9± 14.7	14.95 (**)
PaO_2 (torr)	95.6± 3.75	182± 118	356± 49.0(**)	222± 126	316± 83.1(**)	225± 127	13.37 (**)
$P(A-a)O_2$ (torr)	9.08± 3.74	476± 85.3	341± 32.2(**)	445± 93.2	369± 58.2(**)	443± 92.9	9.72 (**)
$PaCO_2$ (torr)	30.0± 1.55	32.0± 3.88	36.4± 9.14(NS)	32.9± 2.93	37.5± 11.1(NS)	33.0± 3.21	1.67 (NS)
$\overline{PAP}$ (mm Hg)	13.6± 2.62	14.8± 3.61	18.4± 4.02(*)	15.6± 4.01	19.9± 4.24(*)	16.91± 4.24	6.15 (**)
PWP (mm Hg)	4.94± 1.53	5.52± 2.35	9.63± 3.31(**)	5.60± 2.82	7.66± 2.52(**)	5.43± 2.71	18.17 (**)
LVEDP (mmHg)	4.36± 1.51	4.01± 2.74	10.8± 7.77(**)	8.34± 5.05	10.4± 6.73(**)	8.72± 5.04	25.64 (**)
LVSP (mm Hg)	149± 16.8	130± 12.9	139± 18.4(NS)	128± 16.2	139± 19.4(NS)	131± 19.2	1.91 (NS)
dP/dt (mm Hg/sec)	52.4± 11.6	38.4± 11.6	43.6± 12.0(NS)	37.6± 8.81	50.4± 20.4(NS)	40.0± 9.63	0.54 (NS)

Values are mean ± SD. NS: $p>0.05$; *: $0.05>p>0.01$; **: $p<0.01$

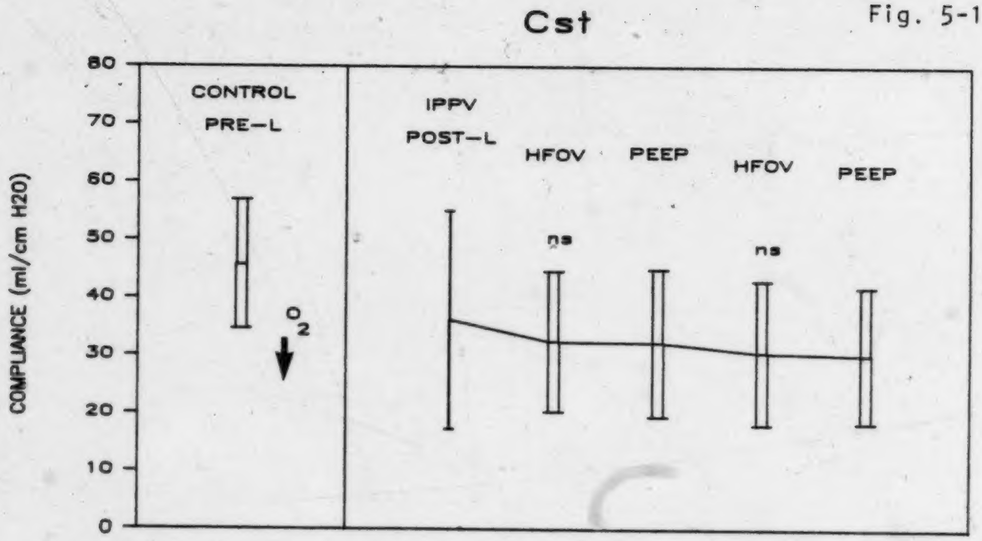


Fig. 5-1

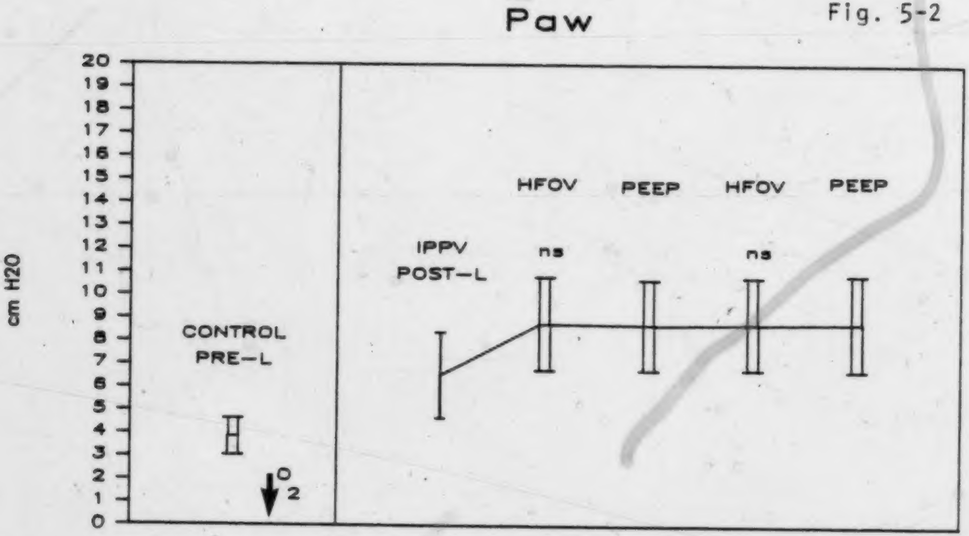


Fig. 5-2

Figures 5-1 and 5-2: Average static lung compliance (top) and mean airway pressure (bottom) changes (±SD) during the control period, IPPV post-lavage and the two HFOV and PEEP periods. Arrow, start $F_iO_2=1$; ns, $p> 0.05$; * $0.05>p>0.01$; **, $p< 0.01$.

Fig. 5-3

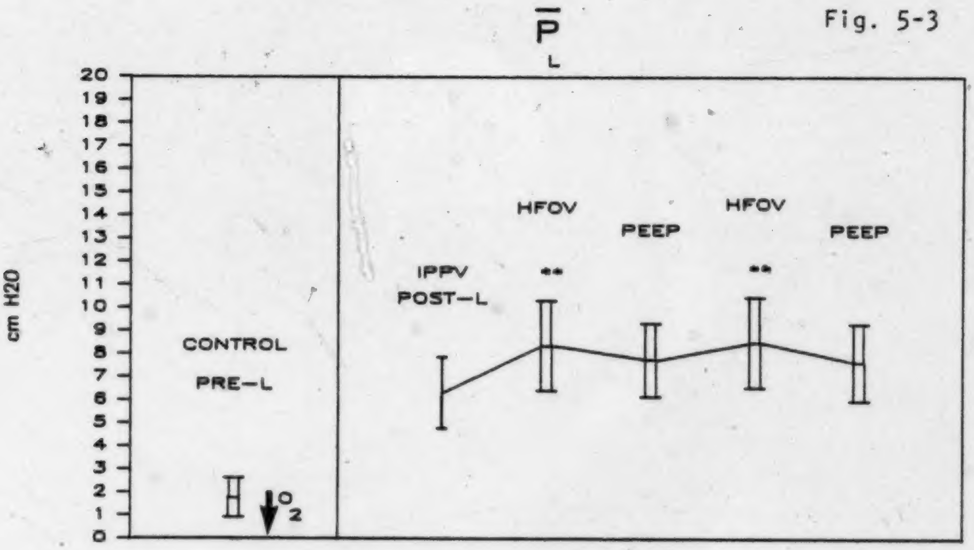
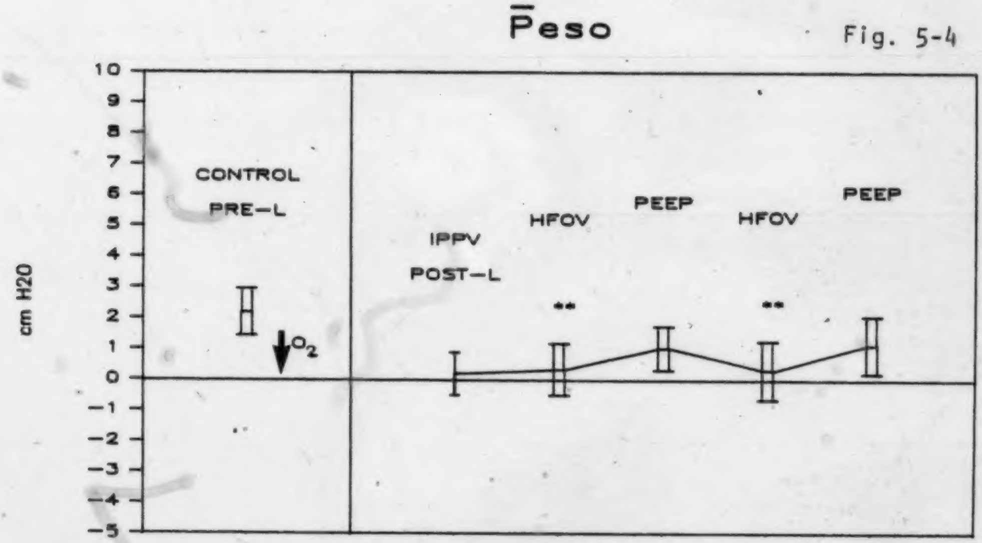


Fig. 5-4



Figures 5-3 and 5-4: Average mean transpulmonary pressure (top) and mean esophageal pressure (bottom) changes (±SD) during the control period, IPPV post-lavage and the two HFOV and PEEP periods. Symbols as in Fig. 5-1.

Fig. 5-5

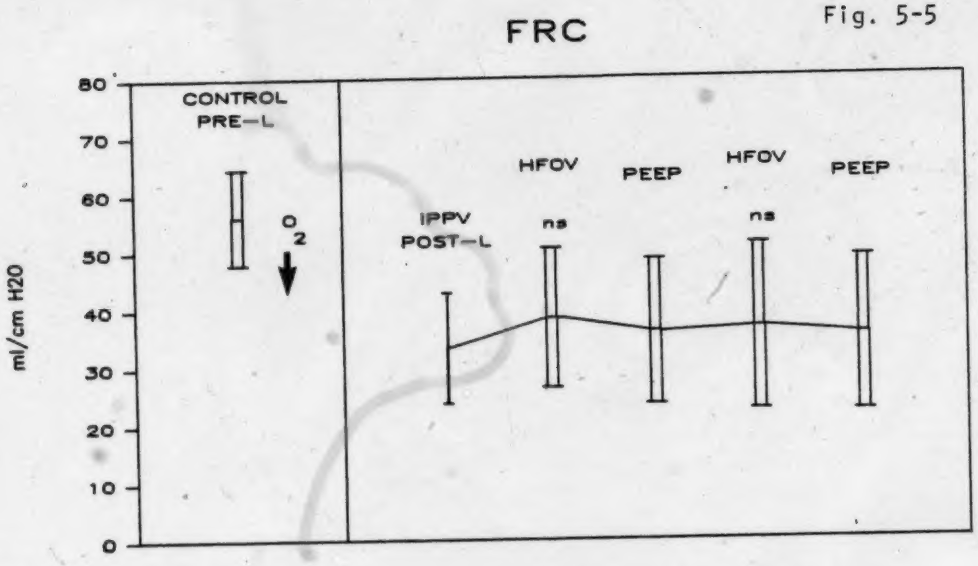
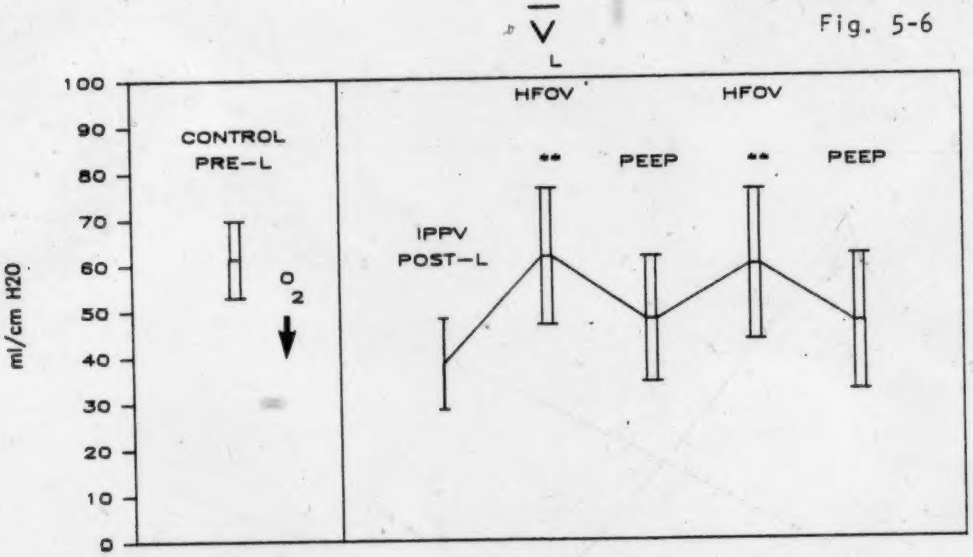


Fig. 5-6



Figures 5-5 and 5-6: Average functional residual capacity (top) and mean lung volume (bottom) changes (±SD) during the control period, IPPV post-lavage and the two HFOV and PEEP periods. Symbols as in Fig. 5-1.

Fig. 5-7

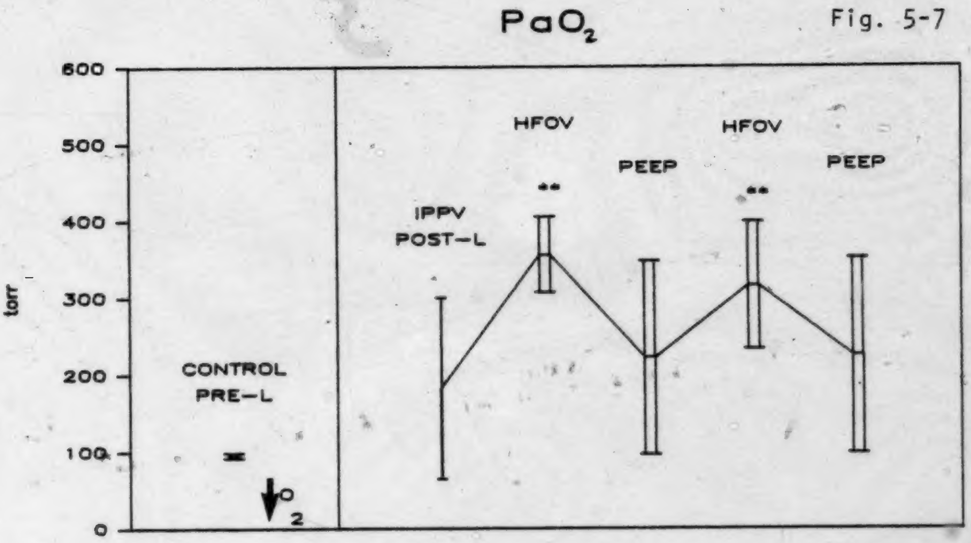
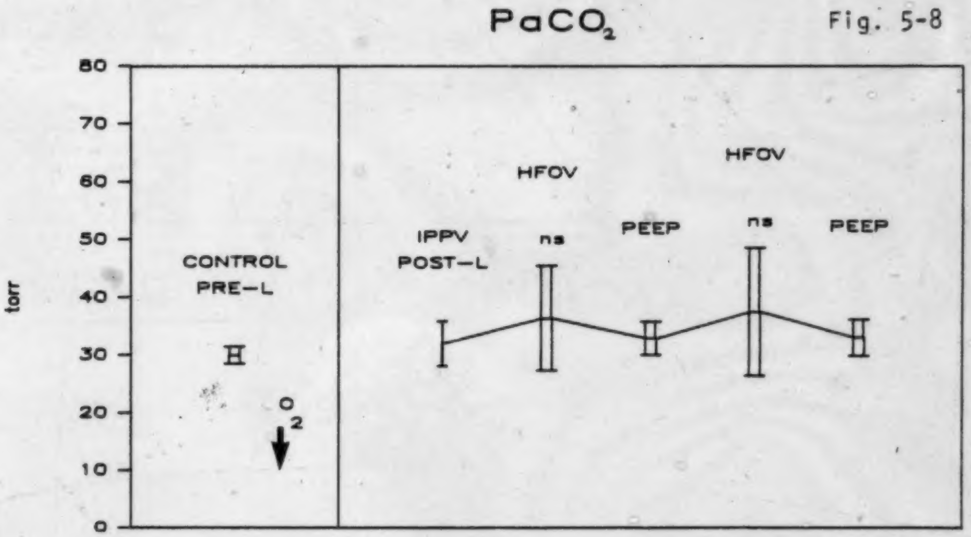


Fig. 5-8



Figures 5-7 and 5-8: Average arterial PO_2 (top) and PCO_2 (bottom) changes (±SD) during the control period, IPPV post-lavage and the two HFOV and PEEP periods. Symbols as in Fig. 5-1.

Fig. 5-9

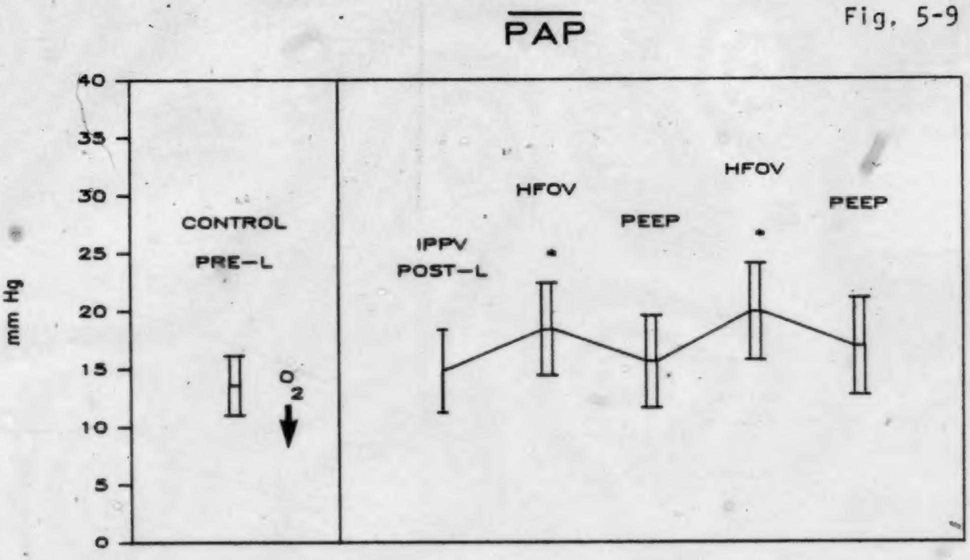
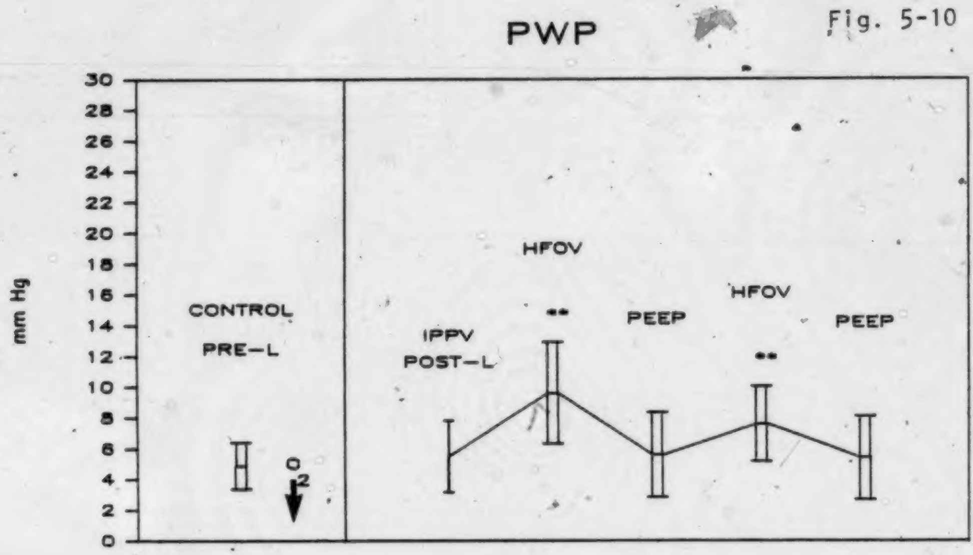


Fig. 5-10



Figures 5-9 and 5-10: Average mean pulmonary artery pressure (top) and pulmonary wedge pressure (bottom) changes (±SD) during the control period, IPPV post-lavage and the two HFOV and PEEP periods. Symbols as in Fig. 5-1.

CHAPTER 6

COLLATERAL VENTILATION DURING HIGH-FREQUENCY OSCILLATION IN DOGS

INTRODUCTION

It is still unclear how high-frequency ventilation (HFV) can achieve gas exchange, the tidal volume being smaller than the anatomical dead space (10). Two main theories have been advanced: that gas exchange is mainly by augmented diffusion (9), and that, despite the small tidal volumes, HFV achieves sufficient bulk movement of gas up and down the airways (11). One mechanism by which HFV could achieve this bulk movement is by enhancing gas transport between lung segments (16), perhaps via collateral channels (20). As there are no studies available on the mechanics of collateral ventilation during HFV, in the present study, resistance (Rcoll) and time constant (Tcoll) of collateral channels were measured during high-frequency oscillatory ventilation (HFOV) and positive end-expiratory pressure (PEEP) with the lungs at the same volume. The measurements were made at several lung volumes during both HFOV and PEEP.

MATERIALS AND METHODS

Eight mongrel dogs weighing 6.5 to 9.2 kg were anesthetized with pentobarbital sodium (30 mg/kg) and intubated with a cuffed endotracheal tube 9 mm i.d. Cuff pressure was kept above 40 cm H_2O. The phrenic nerves were isolated and connected to a Grass stimulator (model SD9) and catheters were inserted into the femoral artery and vein. The animals were placed in the plethysmograph-spirometer system described in Chapter 3 (Fig.6-1), to measure TGV and monitor ΔFRC with the same technique. Measurement Catheters: Three catheters were inserted through airtight holes in the side of the Silastic tubing (Fig.6-2). The first, a short catheter with a Validyne MP45 transducer attached, was used to measure proximal airway pressure (Paw) 4 cm from the proximal airway opening. The amplified transducer output was connected to the physiological recorder, and the Y axis of the X-Y recorder when it was used to calculate TGV as described in Chapter 3. The second, a double-lumen catheter, was threaded down the endotracheal tube. When the outer catheter (o.d. 2.5 mm) entered a small airway, Paw was raised to 30 cm H_2O and the tubing was wedged (as suggested by Woolcock and Macklem, ref.30). The inner catheter's tip protruded 5 mm; its proximal end was connected to the positive side of a P300 Validyne differential-pressure transducer to measure segment pressure (Ps). Compressed air flowed through a calibrated resistance-type flowmeter into the outside catheter ($\dot{V}$coll). For calculations of flow, the pressure drop across the flowmeter's resistive elements (R in Fig. 6-2) was measured with a Statham PM5 differential-pressure transducer whose amplified output went to the physiological recorder, and also to a digital voltmeter (Hewlett Packard model 3430A) to allow precise adjustment of $\dot{V}$coll. The third catheter, used to measure distal airway pressure (Pd), was advanced into the small airways but not wedged. It was connected to another Validyne P300 pressure transducer, as well as to the negative side of the Ps transducer for measuring Ps minus Pd. The catheters for measuring Ps and Pd had occluded distal tips with 6 small side holes in the terminal 1 cm. All pressures (Paw, Pd, and Ps - Pd) were recorded on the Gould strip-chart, and Ps - Pd was also displayed on a digital voltmeter (Gould Digital Display Module, model 13-4611-10) to allow fast and accurate pressure measurements. The criteria for assessing proper wedging of the double-lumen catheter were: resistance to its withdrawal (30); a steady Ps - Pd value that varied with $\dot{V}$coll; rapid oscillations in the Ps - Pd tracing, synchronous with the heart beat; and Ps - Pd = 0 when $\dot{V}$coll was zero.

Experimental Protocol: When preparation was complete, the animal was placed inside the plethysmograph box and the lid was closed. The Harvard respirator was set at a tidal volume of 15 ml/kg and the rate adjusted to give a $PaCO_2$ between 28 and 34 mm Hg. The dogs were ventilated for 1 h at 3 cm H_2O PEEP to allow equilibration of box temperature; then the PEEP level was adjusted to produce a $\overline{P}$d of 10 cm H_2O. After maintenance of this $\overline{P}$d for 15 min, a blood sample was taken for determination of baseline gas values and then the HFOV pump was connected. The oscillator was adjusted to 20 Hz, which induced a $PaCO_2$ value between 28 and 34 mm Hg. In the three largest dogs, the bias flow (air) into the oscillator had to be increased (from 4, to $\leq$ 35 liters/min) to maintain $PaCO_2$ in the desired range. The airway-chamber pressure was adjusted to bring $\overline{P}$d to 10 cm H_2O, and 15 min later another sample was taken for blood-gas determination. The dogs were again ventilated with IPPV, using the Harvard respirator, and then FRC was measured.

Pressure/volume (P/V) curve: The Harvard respirator was restarted after the FRC measurement, and 8-10 min later a static P/V curve for the respiratory system was obtained. For this, the ventilator was disconnected and a 750-ml calibrated syringe was connected in its place. Air was injected through the syringe into the dog's lungs until Paw reached 30 cm H_2O, and then withdrawn. This was done 3 times over 4-6 s. Then the syringe was disconnected for 5-8 s to allow the lungs to reach FRC (the volume changes were monitored with the spirometer). The syringe was reconnected; 4 to 6 increments of air (50 ml for small dogs, 100 ml for larger ones) were injected, allowing 2-3 s for equilibration after each; then the same volumes were withdrawn, again with 2- to 3-s pauses. Measured FRC was used to position the P/V curve on the volume axis.

Measurement of Rcoll and Tcoll: The Harvard respirator was reconnected and the dogs were ventilated for at least 20 min. The box was attached to the spirometer, to monitor changes in lung volume. The Harvard ventilator was replaced by the HFOV pump (set at 20 Hz), for the first measurement of collateral ventilation. Airflow into the double-lumen catheter ($\dot{V}$coll) was started, and adjusted to give a Ps - Pd difference close to 2 cm H_2O (this was usually achieved in 3-5 min). When Ps - Pd had become constant (5-15 s), readings for spirometer volume, $\dot{V}$coll, and Ps - Pd were taken from the digital-display voltmeters. $\dot{V}$coll was stopped, and the exponential decay in the Ps - Pd tracing was recorded at either 50 or 100 mm/s. The oscillator was disconnected, the airway was opened to the atmosphere for 8-10 s to allow the lungs to reach FRC, and the change in spirometer volume was noted. The animal was again ventilated with the Harvard respirator and the PEEP level was adjusted to give the same reading for the spirometer volume (on the digital-display voltmeter) at end expiration as during the steady-state HFOV period. $\dot{V}$coll was adjusted to give a Ps - Pd value close to 2 cm H_2O. The ventilator was stopped at end-expiration; when flow and pressure had stabilized (5-15 s), readings for $\dot{V}$coll and Ps - Pd were taken and the Ps - Pd decay after stopping $\dot{V}$coll was recorded as before. The ventilator was disconnected, to allow the lungs to return to FRC; HFOV was restarted, and the airway-chamber pressure was changed to induce a different lung volume. When a new steady state was reached, the measurements were repeated both during HFOV and at a similar end-expiratory lung volume on PEEP.

These procedures were performed five times on each dog, yielding pairs of measurements (during HFOV and PEEP) of collateral ventilation at five lung volumes. Rcoll, Tcoll and compliance of the occluded segment (Cs^1) were calculated (20), as: Rcoll = (Ps - Pd)/$\dot{V}$coll, Tcoll = time taken for Ps - Pd to decay to 37% of the steady-state value, and Cs^1 = Tcoll/Rcoll.

To obtain accurate readings of Tcoll, the Ps - Pd decay curves were digitized (Hewlett Packard XY digitizer, model 9874A), and stored and analyzed (Hewlett Packard desk-top computer, model 9835). Cardiac artifact was eliminated by a moving-average procedure (4), and the data were fitted into an exponential-decay equation by curvilinear regression analysis with the least-squares method (26). Measured Tcoll (Tcoll') was calculated from the slope (b) of the exponential equation, as Tcoll' = -1/b. As the catheters used to measure the decay of Ps - Pd were long and narrow, and therefore their response time could significantly affect the measurement of Tcoll if Ps - Pd decay were rapid, the catheter/transducer system was tested with a square pressure wave. The time constant of this response (Tcr) was 0.042 s; it was used to correct measured time constants (Tcoll') and obtain the actual Tcoll, using the formula (21): Tcoll = $(\text{Tcoll}')^2 - (\text{Tcr})^2$. As the tip of the wedging catheter was not fixed into place, and thus might have moved when lung volume was changed, thereby altering the size of the wedged segment, the values (Tcoll, Rcoll, and Cs^1) obtained at the different lung volumes were not compared.

Treatment of Data

The static P/V curve of each dog was used to derive the $\overline{\text{P}}$aw expected during HFOV at a given lung volume. For this, each lung volume obtained during HFOV (baseline TGV plus volume change) was plotted on the volume axis of the P/V curve and the predicted airway pressures were read off the pressure axis. Three $\overline{P}$aw values (on the inflation limb, deflation limb, and midway between these points) were derived from the P/V curve for each HFOV volume. $\overline{P}$d values measured during HFOV at each lung volume were compared with the three corresponding derived $\overline{P}$aw values, using a Student's paired t-test. Baseline blood gas values obtained during HFOV and PEEP were also compared with a Student's paired t-test.

For each parameter of collateral ventilation, data from the 8 dogs at each lung volume were pooled. The 40 pairs of values (for HFOV and PEEP) were compared, using Student's paired t-test for assessing significance of differences.

The least-squares method was used for correlating the differences in Rcoll, Tcoll, and Cs^1 values during HFOV and PEEP with the lung volumes at which they were measured. The significance level was set at $p<0.05$. Results are expressed as mean ± SD.

RESULTS

Baseline blood gas values were similar ($p>0.05$) during HFOV and PEEP (Table 6-1). Comparison of the 40 pairs of values for Rcoll, Tcoll and Cs' during HFOV and PEEP (both at the same lung volume) showed Rcoll and Tcoll significantly higher during HFOV but Cs^1 not significantly different (Table 6-2).

Resting lung volume was obtained by adding to the plethysmographic FRC value the increase in lung volume induced by HFOV or PEEP. Rcoll was usually higher during HFOV and tended to decrease as lung volume increased

(Fig.6-3), but comparison of the paired values (pooled data from the 8 dogs) showed no significant correlation between the HFOV/PEEP differences in Rcoll, Tcoll and Cs^1 and the lung volumes at which they were measured. The average differences (±SD) between HFOV and PEEP values were: Rcoll = 0.101 ± 0.142 cm H_2O/ml/s; Tcoll = 0.023 ± 0.036 s; Cs^1 = -0.006 ± 0.073 ml/cm H_2O.

Comparison of $\overline{P}$d values during HFOV with $\overline{P}$aw derived from the static P/V curves at similar lung volumes (Fig.6-4) showed that $\overline{P}$d fell significantly ($p<0.001$) to the right of the deflation curve (1.31 ± 1.53 cm H_2O) and to the left of the inflation curve (2 12 ± 1.47 cm H_2O), but it was not significantly different from the calculated midpoint between these curves.

DISCUSSION

The present technique for measuring collateral resistance and the time constant of the collateral channels is similar to Hilpert's (12) as detailed by Menkes and Traystman (20), with minor modifications. Hilpert placed glue at the tip of the double-lumen catheter, to prevent its displacement; this was not done in present experiments. In preliminary trials it was found difficult to dislodge the catheter when it was wedged at high lung volume as suggested by Woolcock and Macklem (30), and unwedging it resulted in a sudden drop in Ps - Pd to near zero when $\dot{V}$coll was on. Secondly, glueing the tip into position would have hampered occasional removal of the catheter to clear obstruction by secretions. In the present study, spontaneous dislodgement was not observed. However, as repeated changes between HFOV and PEEP raised this possibility, Rcoll and Tcoll obtained at different lung volumes were not compared even though, in 4 of the 8 dogs, it was observed as others have (30) that Rcoll and Tcoll decreased as lung volume increased.

Digital-display voltmeters were used to obtain simultaneous $\dot{V}$coll and

Ps - Pd readings and improve the accuracy of measurements. A digitizer with a computer that removed the cardiac artifact by a moving-average method (4) was used to calculate the slope of the Ps - Pd decay, increasing the accuracy of Tcoll calculations. The difficulty in calculating Tcoll from raw Ps - Pd curves is apparent in the tracings reproduced in Fig.3b of the report by Menkes and Traystman (20).

Although the P300 transducer used to measure Ps - Pd had a very small internal volume (0.57 ml), the time constant (63% response time) of the catheter/transducer system was 0.042 s, which was similar to the fastest Tcoll' measured (0.054 s). Therefore, correction for Tcr was critical. Woolcock and Macklem (30) used a Ps catheter of similar size but with a Sanborn transducer that has a relatively large internal volume (3.42 ml; Ref.14). Thus the time constant of their catheter/transducer system was doubtless larger than the 0.042 s measured for the present system; and, as they did not use Tcr to correct Tcoll', there may have been a substantial error, especially in their assessment of short time constants.

The present findings suggest that resistance to flow through collateral channels is increased during HFOV. It was felt that this was not caused by an artifact of the measurement method. As lung volume is a major determinant of collateral ventilation (20), Rcoll and Tcoll were measured at the same lung volumes during HFOV and PEEP. Also, the $\dot{V}$coll-induced pressure difference (Ps - Pd) across the collateral channels was maintained at 2 ± 0.3 cm H_2O during both HFOV and PEEP, to cause similar distention of the wedged segment.

When the three dogs larger than 8 kg were ventilated, a low $PaCO_2$ could not be maintained with the standard HFOV setting (20 Hz, with the bias flow at 4 liters/min). However, when the bias flow was increased up to $\leq$ 35 liters/min, with airway-chamber pressure adjusted to maintain $\overline{P}$aw at 10 cm

H_2O, the $PaCO_2$ fell to the range achieved in the smaller dogs. The higher $PaCO_2$ in the larger dogs during HFOV probably indicates that 'alveolar ventilation' induced by the oscillator was insufficient to eliminate the weight-dependent larger CO_2 production, requiring enhancement of CO_2 removal by increased bias flow (15). Alternatively, the collateral pathways may not have been fully developed (18) in these three animals, which were also the youngest (< 1 yr). If the latter is correct, collateral ventilation could be important during HFOV (3) and the effects of lung immaturity on the efficiency of HFOV should be considered.

There are several possible explanations for the higher collateral resistance during HFOV than with PEEP. Results of earlier HFOV experiments (2) with the same oscillator indicated a lower mean pressure in the proximal airway than in the alveoli, as has been suggested by others (5,25). This pressure gradient could result in less distention of the Lambert and Martin channels (20) than during static conditions (PEEP), when airway and alveolar pressures are equal. However, the pressures in the various airway generations are not known, or also whether small changes in pressure can affect the diameter of collateral pathways. Moreover, there is disagreement over the contributions by bronchiolar and alveolar pathways in collateral ventilation (20). It is unlikely that this mechanism plays a significant role.

Changes in surface tension, also, may affect collateral ventilation (19), although available data suggest that high-frequency ventilation does not alter surfactant activity (8). The present HFOV system increases pulmonary arterial pressure (1), but the reported influence of the pulmonary circulation on collateral ventilation seems due to changes in CO_2 or to pulmonary edema (20). Any increase in PCO_2 decreases Rcoll (27,28), but the HFOV and PEEP baseline $PaCO_2$ values were not significantly different (Table 1), and the short time between HFOV and PEEP measurements would not have allowed much change. Similarly, hypoxia increases Rcoll (28), but the 5—15 s of apnea required to make the Rcoll measurements during PEEP would depress PO_2 only slightly, and, if anything, increase Rcoll. Changes in local ventilation/perfusion ratios could have influenced local gas concentrations in the present studies, and consequently Rcoll. The experimental setup did not allow for control of this variable.

A possible explanation for the present findings is that, during HFOV, a vagally mediated reflex increases the resistance of collateral channels. It has been reported that HFOV increases the discharge from irritant receptors in the airways (31). As these receptors can induce reflex bronchoconstriction via the vagus (22), and vagal discharge can increase Rcoll (23,24,29), HFOV may increase Rcoll by stimulating these irritant receptors. This is supported by the finding that high-frequency ventilation increases bronchomotor tone, at least in the large airways (6). However, the effects of vagotomy on collateral resistance during HFOV, which might help establish whether the vagus is involved in the observed changes in Rcoll, are not known.

Tcoll, also, was higher during HFOV. This was probably due to the increased Rcoll, as Cs^1 did not change ($Tcoll = Rcoll \times Cs^1$). The calculated compliances of the wedged segment (Cs^1) during HFOV and PEEP were similar, suggesting that the lungs' elastic characteristics are almost the same during these two conditions. This is supported by the position of the $\bar{P}d$ values at the midline between the inflation and deflation part of the P/V curves (Fig.6-4).

In 1980, Bohn et al. (3) showed that HFOV can maintain adequate ventilation with tidal volumes smaller than dead space, but the mechanism of gas exchange during this mode of ventilation is still not clear. Ventilation during HFOV may be achieved by enhanced diffusion (9) or by HFOV-induced bulk transport of gas (11). The latter might be facilitated by intersegmental gas movement (16), whose existence is suggested by the uneven movement of lung surface under a strobe light (17) and irregular displacement of intraparenchymal lead markers (13) during HFOV. An important pathway for this intersegmental gas transport may be through collateral channels. The relative inefficiency of gas exchange during HFOV in pigs (3), which have high Rcoll (20), would be consistent with an important role for collateral ventilation.

It is concluded that during HFOV the resistance to gas flow through collateral channels is increased but that gas exchange via this route may still be important. Thus, drugs that decrease Rcoll (20) might enhance the efficacy of HFOV.

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TABLE 6-1. *Baseline blood gas values of each dog, obtained during the control periods*

	PEEP		HFOV	
Dog #	$PaCO_2$	PaO_2	$PaCO_2$	PaO_2
1	29.4	97.2	30.4	101.3
2	32.1	95.7	28.6	110.3
3	34.0	85.9	31.6	87.5
4	32.5	94.8	31.7	94.4
5	29.1	92.7	32.8	88.8
6	33.4	94.2	31.4	90.5
7	32.8	98.2	33.3	97.9
8	30.4	92.9	29.3	94.4
Mean ± SD	31.7±1.8	94.0±3.8	31.1±1.6	95.6±7.5

TABLE 6-2. Effect of HFOV and PEEP at the same lung volume on indices of collateral ventilation (mean ± SD, n = 40*)

	Rcoll (cm H_2O/ml/s)	Tcoll (s)	Cs[1] (ml/cm H_2O)
HFOV	0.710 ± 0.324	0.185 ± 0.100	0.277 ± 0.166
PEEP	0.609 ± 0.306	0.161 ± 0.084	0.284 ± 0.176
P	<0.001	<0.001	>0.05

* Mean values were calculated from individual values for 8 dogs at 5 lung volumes, which were different for each animal.

Fig. 6-1

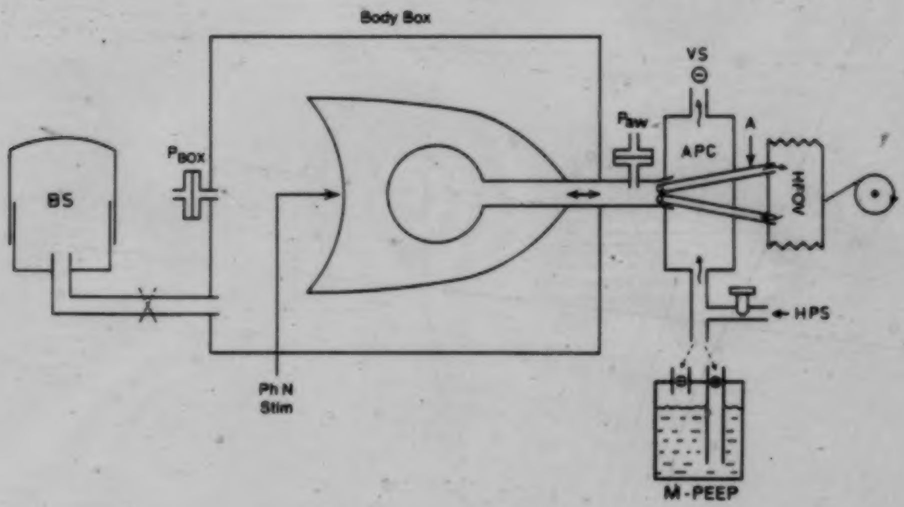
Body Box
BS
P_{BOX}
P_{aw}
VS
A
APC
HFOV
HPS
PhN Stim
M-PEEP

Fig. 6-2

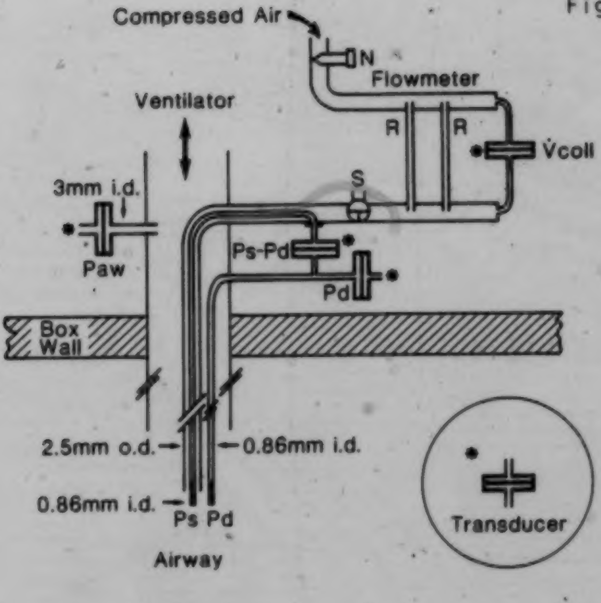
Compressed Air
N
Flowmeter
Ventilator
R
R
$\dot{V}$coll
S
3mm i.d.
Paw
Ps-Pd
Pd
Box Wall
2.5mm o.d.
0.86mm i.d.
0.86mm i.d.
Ps Pd
Airway
Transducer

Figure 6-1: Diagram of the HFOV circuit and plethysmograph. Symbols as in Fig. 4-1. Fig.6-2: Diagram of the set-up for studies of collateral ventilation. Catheters and transducers for measuring pressures: Paw, airway; Ps, segmental; Pd, distal. $\dot{V}$coll, transducer for measuring collateral flow. N, needle valve; R, flowmeter's resistive elements; S, stopcock.

Fig. 6-3

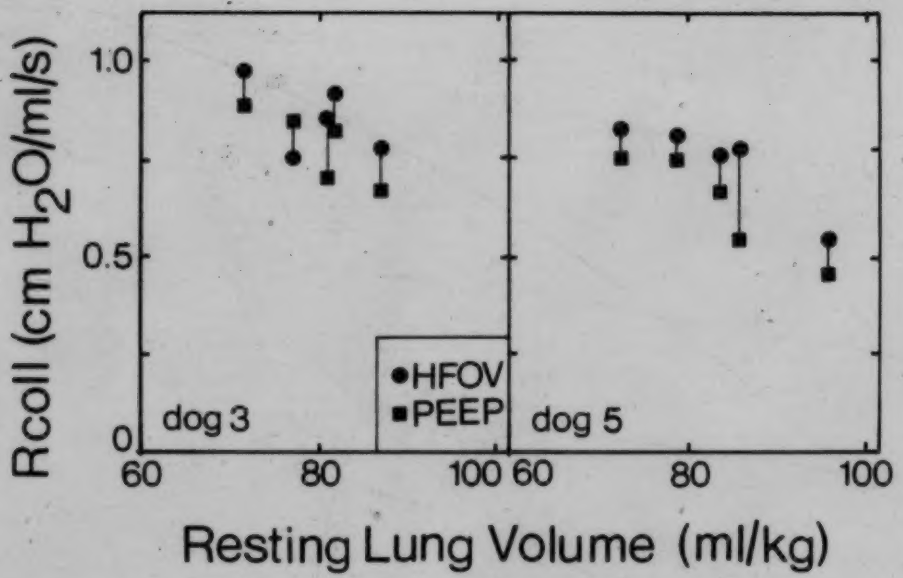

Fig. 6-4

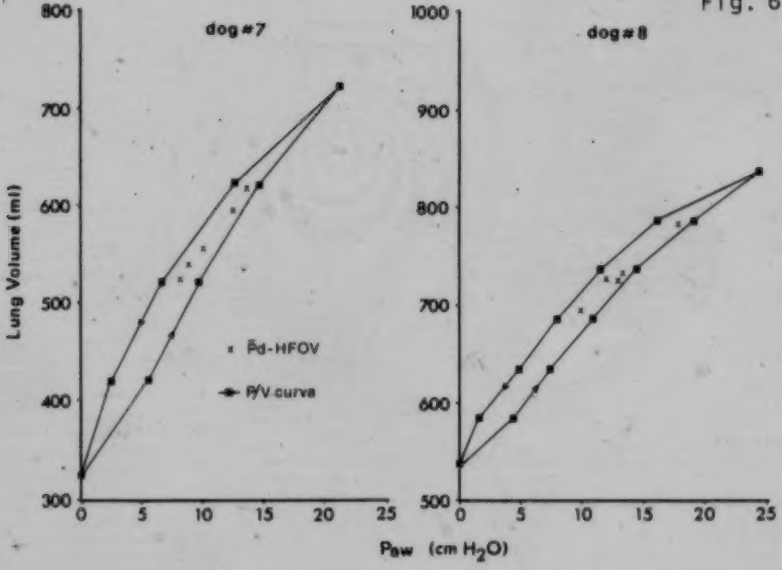

Fig.6-3: Collateral resistances (Rcoll) in two dogs, measured at different lung volumes during HFOV and PEEP. Fig.6-4: Static pressure/volume curves of two dogs, and mean distal airway pressures during HFOV.

CHAPTER 7

TRACHEAL MUCOUS TRANSPORT OF LARGE AND SMALL PARTICLES DURING HIGH FREQUENCY OSCILLATORY VENTILATION IN DOGS

INTRODUCTION

High-frequency ventilation has received much attention in recent years, and has been used clinically(4,5); as yet, there is not enough data to establish its safety. The effect of HFV on the pulmonary mucociliary function has not been well defined. There are several reports of large amounts of secretions in the airways during HFV (1,11,17,19), and it has been suggested that this could be due to an augmented mucus production and/or enhancement in mucus flow(19). There are two reports on mucociliary function during HFV, both in anesthetized dogs: in the first, the authors concluded that mucociliary transport was preserved, but no data was presented(15). The second report found satisfactory tracheal mucous transport rates (TMTR), but abolished lung clearance(19); however, no comparisons were made with SB or IPPV.

In the present experiments, TMTR of two different radiolabelled markers were measured during HFOV, IPPV and SB. The markers were chosen to cover a range of sizes which could be encountered clinically as pollutants.

MATERIALS AND METHODS

Ten mongrel dogs were used in these studies: four animals (23.1 ± 2.2 kg) in the 12 experiments comparing SB with IPPV, and six (8.0 ± 0.8 kg) in the 19 HFOV/IPPV comparisons. Each animal was studied several times, and at least a week elapsed between two consecutive studies in the same dog.

Measurement of the tracheal mucous transport rates: The animals were anesthetized with pentobarbital (30 mg/kg i.v.); additional doses of barbiturate were administered when necessary to maintain a light level of anesthesia. The dogs were studied one hour after anesthesia to allow for the acute effects of pentobarbital to dissipate. The experiment proceeded as follows: a 8- or 9-mm i.d. endotracheal tube was inserted and the inflated cuff (high compliance) positioned just below the vocal cords. Immediately thereafter, a few droplets of a saline suspension of both Dowex anion-exchange particles and sulfur colloid were deposited on the posterior membrane of the lower trachea by a user-designed double-lumen pipette which allowed both particles to remain separate until deposited in the trachea (Fig.7-1). The Dowex particles were spherical and uniform in size and had a mean diameter of 50 μm; they were radio-labelled with ^{125}I. Sulfur colloid particles were irregular in shape with sizes ranging between 0.2 and 1.0 μm; they were labelled with ^{99m}Tc. The usual amount of radioactivity deposited was approximately 180 μCi for ^{125}I and 160 μCi for ^{99m}Tc, and the volume ranged from 30 to 50 μl for each type of particle suspension.

Radioactivity was measured externally with a collimated sodium iodide crystal mounted on a rectilinear scanner which moved back and forth over the long axis of the trachea (Fig.7-2) at a constant speed (40 mm/min). The detector was connected to a dual-channel gamma analyzer with a two channel ink recorder (Picker Nuclear, dual probe model 2000). TMTR of the particles were calculated from the recorded radioactivity histograms, by the change in their positions over time (Fig.7-3). Immediately after the radioactive suspensions were deposited, the animals were connected to the respiratory circuits described below, and scanning commenced. The starting mode of ventilation was assigned at random. When at least one radioactive peak had been detected to be moving for 4 to 6 consecutive scanner traverses, the animal was switched to a second mode of ventilation (Fig.7-4). Similarly, when movement of peaks could be detected in 4 to 6 consecutive scans, the animal was switched back to the first mode of ventilation. This process was repeated until the radioactive peak stopped at the upper tracheal level.

Respiratory circuit for spontaneous breathing versus conventional ventilation: This respiratory circuit (Fig.7-5) was designed in such a way as to allow the dog to either breathe spontaneously or be ventilated with a volumetric respirator (model 607, Harvard Apparatus Co., Millis, MA) with a tidal volume of 15 ml/kg body weight and at a rate 15 breaths/min (IPPV). When the animals were either on SB or IPPV, the inspiratory air was maintained at a similar temperature (32—35°C) and a relative humidity >95%. It took less than four seconds to switch the animal from one mode of ventilation to the other (IPPV or SB).

Respiratory circuit for conventional versus high-frequency ventilation studies: This circuit (Fig.7-6) had an arrangement for IPPV similar to the one described above. In addition, the bellows oscillator was incorporated into the circuit with an arrangement similar to the one described in Chapter 2. The 2 oscillator catheters and endotracheal tube tip were enclosed on a 62.5-ml chamber which was continuously flushed with 15 L/min of warm humidified air (32—35 °C, relative humidity >95%). The oscillator was set at a frequency of 25 Hz; the bias flow (4 L/min) was warmed and humidified (32—35°C, relative humidity >95%). In preliminary experiments it was found that the dogs could be adequately ventilated at this setting. The circuit allowed for switching the animal from IPPV to HFOV (or vice versa) in less than four seconds.

Statistical analysis: The linearity of the movement of each peak was assessed by linear regression analysis(23), by plotting the change in distance on the Y axis and the time elapsed on the X axis. The significance level for the correlation coefficients was established at $p<0.05$. The values of TMTR were obtained from the slope of the regression lines (with significant correlation). They differed widely from dog to dog (Figs.7-7 and 7-8). Thus a normal distribution of the values could not be assumed and a nonparametric statistical method was chosen. The TMTR on different modes of ventilation were compared with a χ^2 test on a 3 x 2 contingency table(23). The significance level was established at $p<0.025$ because TMTR had been calculated statistically.

To rule out the possibility that one type of particle or one ventilatory mode had preferentially affected the initial movement of a radioactive peak, another χ^2 analysis (2 x 2 contingency table) was performed. In this analysis, a comparison was made firstly between the two different particles, taking into account the number of intial peaks of each that were observed, and secondly, between the different ventilatory modes with regard to the number of times a radioactive peak started moving during each type of ventilation.

RESULTS

Spontaneous breathing versus conventional ventilation: On a total of 31 occasions the ventilatory modes could be switched at least once, while the radioactive peaks were moving (Table 7-1). From these, 72 TMTR were calculated (26 with sulfur colloid and 46 with Dowex particles), and 42 comparisons were made between SB and IPPV (in several instances the animal could be switched back and forth to different ventilatory modes more than once). A wide variation of TMTR was obtained (Fig.7-7) and TMTR were usually altered when the type of ventilation mode was changed, but no clear trend was observed: statistical analysis showed that the changes induced by the two ventilatory modes were statistically equivalent ($p>0.10$, Table 7-2). Similar findings were obtained when the two particle sizes were analyzed separately: ^{99m}Tc-sulfur colloid, $p>0.60$; (Table 7-3) ^{125}I-Dowex, $p>0.20$. Also, a comparable number of peaks of each particle type started moving at the lower trachea ($p>0.90$, Table 7-4) and the two ventilatory modes had a similar influence on the number of moving peaks ($p>0.20$).

High frequency oscillation versus conventional ventilation: A total of 48 runs were completed and 101 TMTR obtained. From these, 53 comparisons were made between HFOV and IPPV (Table 7-1). The variation in TMTR was similar to the previous group (Fig.7-5). Statistical analysis of the data showed an equivalent effect of both ventilatory modes on TMTR ($p>0.05$, Table 7-5). A separate analysis of each type of particles also showed similar effects of the different modes of ventilation: ^{99m}Tc-sulfur colloid, $p>0.50$; ^{125}I-Dowex, $p>0.20$ (Table 7-3). Likewise, the ventilatory mode and the particle type did not influence the number of peaks that started moving ($p>0.10$ and $p>0.80$ respectively, Table 7-4).

DISCUSSION

Mucociliary function is a crucial lung defense mechanism in normal humans(6); in mechanically ventilated patients who have impaired cough, it may be of even greater importance. Unfortunately, little is known about mucociliary function in the critically ill patient. Before HFV is accepted for clinical use both its short- and long-term safety have to be validated. In the present study, the acute effects of conventional ventilation and HFOV on the tracheal transport rates of radiolabelled particles were compared. Several methods have been employed to assess in vivo mucous transport mechanisms(25). They include the use of teflon discs viewed by cinebronchoscopy(24), carbon-licopodium particles viewed through transilluminated tracheas(12), and radiolabelled albumin microspheres(26) or resin beads(21) followed by scintiscanning. The technique used in the present studies has an added advantage over the others as it provides the simultaneous measurement of the TMTR of two different markers, and in this case particle sizes of 50 µm and less than 1 µm in diameter were used. These sizes were chosen to cover a range of particulate pollutants that could be encountered in a hospital environment, i.e.: bacteria, dust and aerosols(2). It was postulated that a mechanical interaction of the ventilation with the particles should preferentially affect the larger sizes. No such effect was observed in the present experiments, during either IPPV or HFOV.

In the design of this study, the fact that the movement of particles as assessed by the scanning method is linear as evidenced by the regression analysis(7) was utilized. The change in the mode of ventilation was done once a linear displacement of a radioactive peak was observed. Therefore, the effect of the ventilatory mode, if any, could be assessed by a variation in the rate of movement of the radioactive peaks. Indeed, such a variation was observed in many instances, but no particular ventilatory mode showed a tendency to preferentially increase or decrease TMTR, or to impede the initial movement of the peaks. The mechanical effect of abruptly switching the ventilation could have changed the tracheal path that the particles were following and thus the TMTR. Other factors could also affect the results in this study: the endotracheal tube itself may impair mucocilciary transport(20), although studies of this factor have produced conflicting results(8-10). In the present experiments, the dogs showed good particle clearance even after more than three hours with the cuff inflated. It has been suggested that barbiturate anesthesia decreases TMTR(3,16), but again reports are conflicting (8,13,18). Despite the potential factors that might alter TMTR, the randomization employed in the present experiments and the brief periods studied, should have prevented any of these factors from prevailing during a particular ventilatory mode.

The effects of artificial ventilation on mucociliary function are not well known and some experiments suggest that it may be depressed during IPPV(10). The present study suggests that in intubated animals breathing warmed and humidified air, the effects of IPPV on TMTR is not different from spontaneous breathing. It was also found that IPPV and HFOV influenced TMTR in a similar way. Klain et al. have also reported that the effects of HFV (in this case HFJV) and IPPV are similar(15). These authors measured TMTR by the movement of dye in the trachea of dogs, observed by cinebronchoscopy. Unfortunately, their study has been published only as in abstract form, and no data or statistical analysis are available. In a recent report, McEvoy et al. found preserved TMTR (assessed with a gamma camera) after more than 4 h of IPPV or HFOV(19). However, no baseline TMTR measurements during IPPV or SB are compared with those obtained during HFOV.

The present experimental design was intended to assess the acute interaction of ventilation with TMTR. A chronic study might not necessarily produce the same results, and such a study is needed to establish the safety of long-term HFOV. The wide range of TMTR in the same subject and between individuals would make such a study difficult. In preliminary trials, it was found that the present HFOV system induced a long-lasting apnea (often over 1 min) in the dogs after the pump was turned off. This prevented comparing directly HFOV with SB, because the metabolic disturbances induced by the period of apnea could make such a comparison invalid.

In a recent publication, King et al. reported an enhanced tracheal mucous clearance rate during externally applied chest wall compression at high frequency(14). The physical interaction of this mode of ventilation with the respiratory system can be expected to differ greatly from that of HFOV, and this might explain, at least in part, the discrepancies with the present findings. Also, King et al. used a fiberoptic bronchoscope to monitor TMTR; the effect of airflow obstruction by the bronchoscope might have influenced their results.

HFOV could have some specific effects on TMTR. For example, during HFOV gas velocity is much higher than during IPPV, and different velocity profiles develop in the airways(22). Under these conditions, the transport of particles by the mucous lining layer could be directly influenced. Also, cilia beat at around 20 Hz(25) and their movement could be affected by HFOV oscillating at a similar frequency. Moreover, there are reports which suggest that mucus production is altered during HFOV(6), although the exact mechanism (mechanical, metabolic, neural, etc.) is not known. Neither the magnitude nor the sudden onset of the effects of HFOV on the mucociliary apparatus was sufficient in the present study to induce a significant difference in TMTR between HFOV and IPPV.

In conclusion, this study suggests that the acute effects of HFOV and IPPV on the canine tracheal transport of particles are not different. Moreover, two sizes of particles were affected similarly by both modes of ventilation. The findings during spontaneous respiration were similar to those on IPPV. It is unlikely that during short-term use HFOV is any more detrimental to this lung defense mechanism than IPPV.

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TABLE 7-1: General data related to the experiments (mean ± SD)

	SB/IPPV	IPPV/HFOV
Dogs	4	6
Dogs weight	23 ± 2.2	7.98 ± 0.8
Experiments per dog	3.0 ± 0.8	3.3 ± 1.0
Total Runs	31	48
Runs per experiment	2.8 ± 1.2	2.7 ± 1.0
Peaks per effective run	2.2 ± 1.4	1.8 ± 0.7
Total successful pairs	42	53

TABLE 7-2: Spontaneous breathing versus IPPV experiments

Particle	Ventilation Mode	Peaks	Average Speed ± SD (mm/min)	Coefficient of Variation(%)	Speed Range (mm/min)
Dowex	IPPV	24	10.0 ± 5.1	50	4.1 - 23.7
	SB	22	10.0 ± 5.5	55	3.6 - 25.3
Sulfur Colloid	IPPV	14	11.3 ± 3.9	34	5.0 - 16.4
	SB	12	10.4 ± 4.0	39	5.7 - 17.5
All Dowex		46	10.0 ± 5.2	52	3.6 - 25.3
All Sulfur Colloid		26	10.9 ± 3.9	36	5.0 - 17.5
	All IPPV	38	10.5 ± 4.6	44	4.1 - 23.7
	All SB	34	10.2 ± 5.0	49	3.6 - 25.3
TOTAL		72	10.3 ± 4.8	46	3.6 - 25.3

TABLE 7-3: Effect of particle size onTMTR

a) Spontaneous breathing versus IPPV studies

Particle	n pairs	χ^2	p
^{99m}Tc Sulphur colloid	15	0.875	>0.60
^{125}I Dowex	27	2.477	>0.20
TOTAL	42	4.001	>0.10

b) HFOV versus IPPV studies

Particle	n pairs	χ^2	p
^{99m}Tc Sulphur colloid	22	1.204	>0.50
^{125}I Dowex	31	2.849	>0.20
TOTAL	53	5.517	>0.05

TABLE 7-4: Comparison of starting movements

Experiment	Comparison	n	χ^2	p
SB/IPPV	Dowex vs Sulphur colloid	30	0.063	>0.90
SB/IPPV	SB vs IPPV	30	2.802	>0.20
HFOV/IPPV	Dowex vs Sulphur colloid	49	0.692	>0.80
HFOV/IPPV	HFOV vs IPPV	49	3.232	>0.10

TABLE 7-5: IPPV versus HFOV experiments

Particle	Ventilation Mode	Peaks	Average Speed ± SD (mm/min)	Coefficient of Variation(%)	Speed Range (mm/min)
Dowex	IPPV	29	19.1 ± 8.5	43	4.4 - 37.7
	HFOV	29	16.5 ± 7.5	46	5.6 - 32.9
Sulfur Colloid	IPPV	22	20.1 ± 7.3	36	7.8 - 30.7
	HFOV	21	19.5 ± 7.2	38	7.7 - 36.3
All Dowex		58	17.8 ± 8.1	48	4.4 - 37.7
All Sulfur Colloid		43	19.4 ± 7.2	35	7.7 - 36.3
	All IPPV	51	19.5 ± 8.0	40	4.4 - 37.7
	All HFOV	50	17.5 ± 7.4	43	5.6 - 36.3
TOTAL		101	18.5 ± 7.5	40	4.4 - 37.7

Fig. 7-1

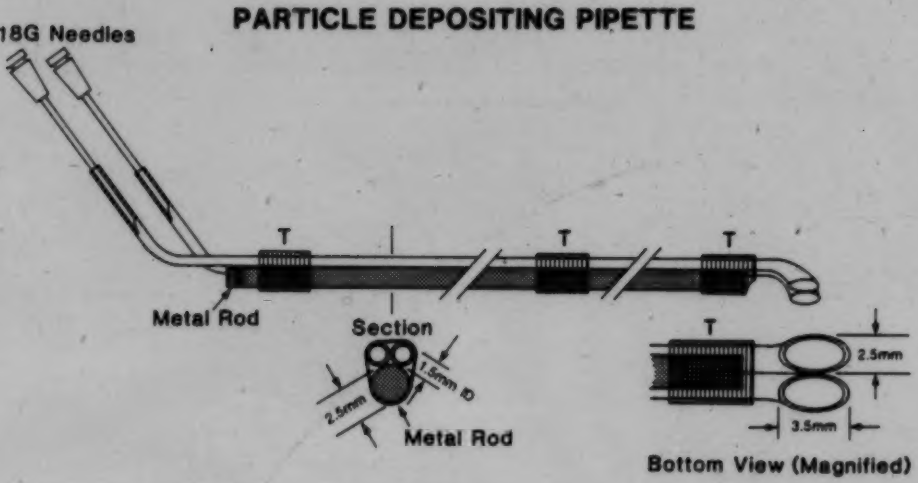
PARTICLE DEPOSITING PIPETTE
18G Needles
T
T
T
Metal Rod
Section
1.5mm ID
2.5mm
Metal Rod
T
2.5mm
3.5mm
Bottom View (Magnified)

Fig. 7-2

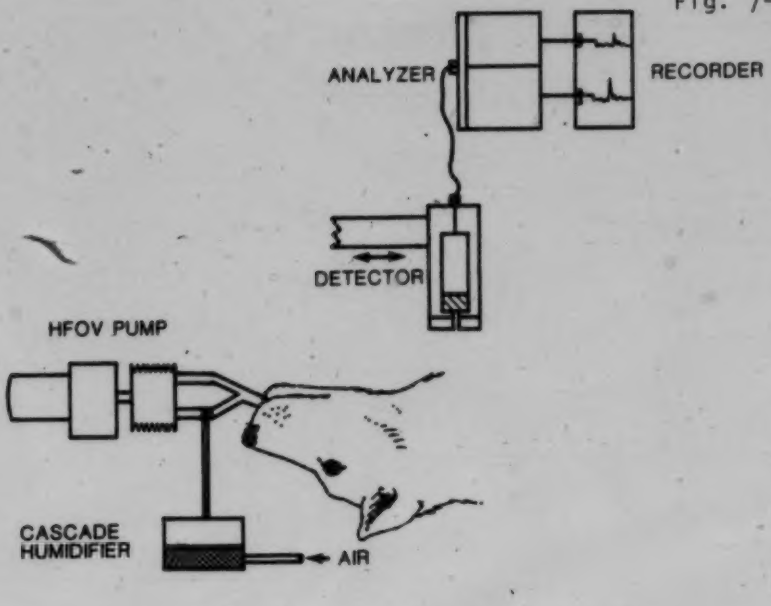
ANALYZER
RECORDER
DETECTOR
HFOV PUMP
CASCADE HUMIDIFIER
AIR

Figure 7-1: Dual-channel pipette used for particle deposition. T, plastic tape. Details: center, crossectional view; bottom right, tip of the pipette. Figure 7-2: Diagram of the setup for the simultaneous measurement of transport rates of two sizes of radiolabelled particles.

Fig. 7-3

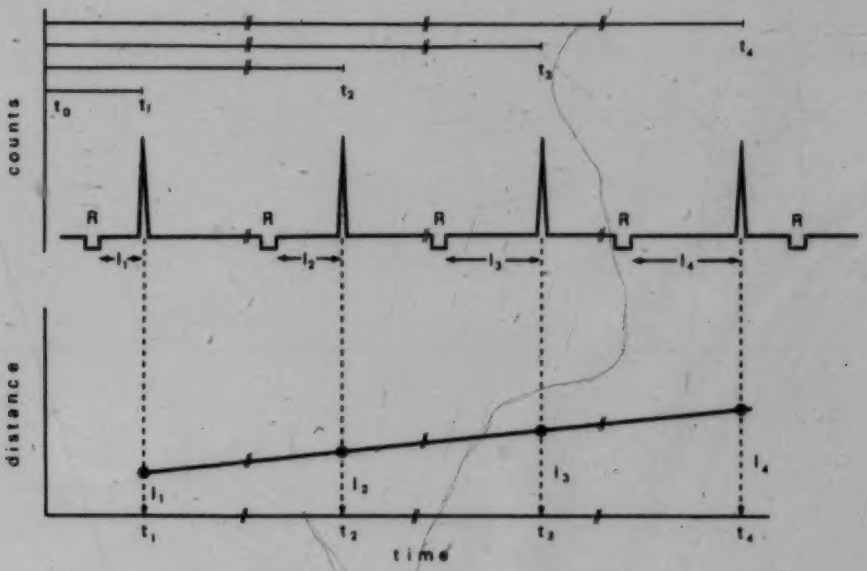
counts
distance
time
R
t0
t1
t2
t3
t4
I1
I2
I3
I4

Fig. 7-4

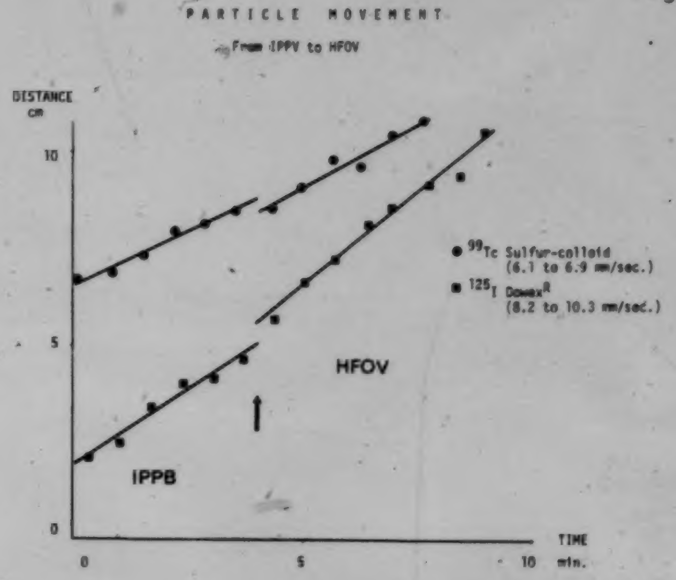

Figure 7-3: Diagram showing the method used to calculate TMTR from radioactivity histograms. I_1-I_4, distances; t_0-t_4, times; R, position mark. Figure 7-4: Example of movement of two particle types and change from IPPV toHFOV. Arrow, change ventilatory mode.

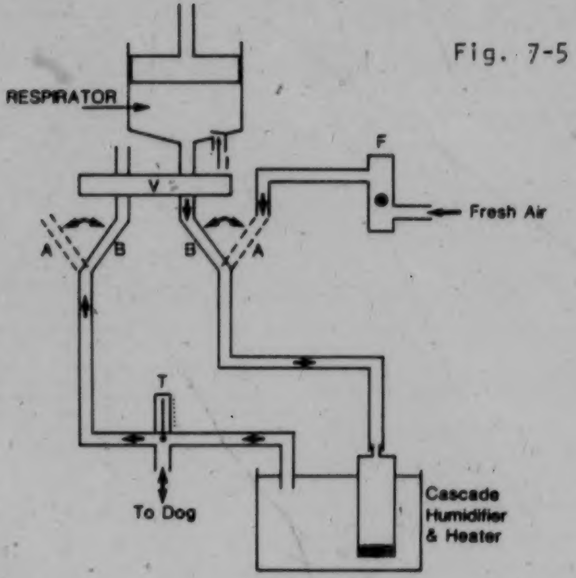
RESPIRATOR
I
V
F
Fresh Air
A
B
B
A
T
To Dog
Cascade Humidifier & Heater

Fig. 7-5

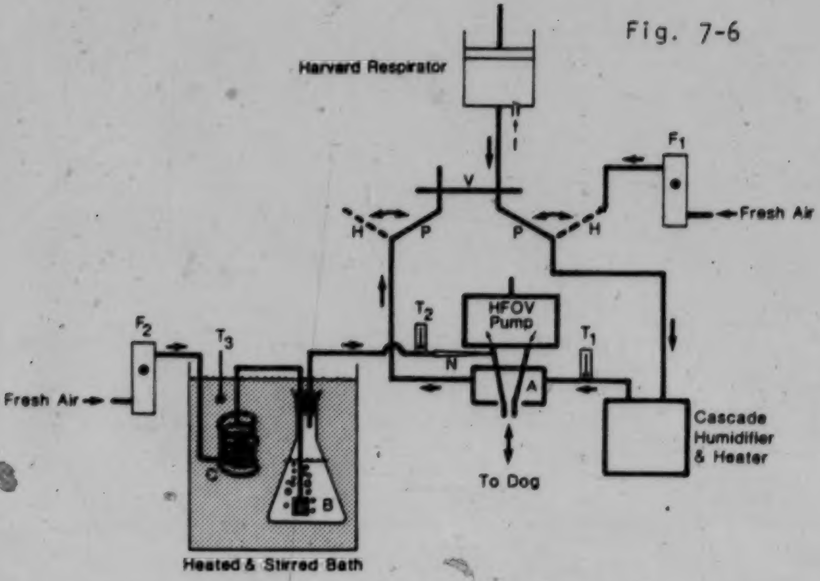
Harvard Respirator
I
V
F$_1$
Fresh Air
H
P
P
H
T$_2$
HFOV Pump
T$_1$
F$_2$
T$_3$
N
A
Fresh Air
C
B
To Dog
Cascade Humidifier & Heater
Heated & Stirred Bath

Fig. 7-6

Figure 7-5: Circuit diagram for spontaneous breathing (position A) and IPPV (position B) studies. F = flow meter; I = IPPV inlet; T = thermometer; V = IPPV valves. Figure 7-6: Circuit diagram for HFOV (position H) and IPPV (position P) studies. A = HFOV conditioning chamber; B = bubble humidifier; C = heated coil; F_1,F_2 = flowmeters; I = IPPV inlet; N = 14 G needle; T_1,T_2,T_3 = thermometers; V = IPPV values.

Fig. 7-7

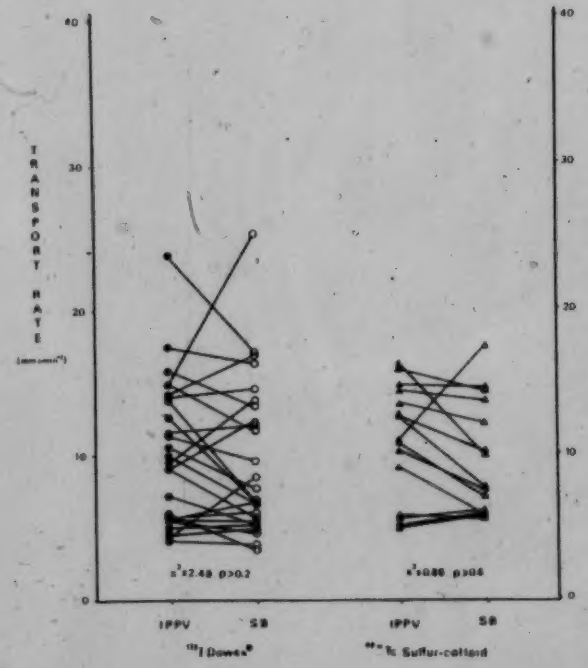

Fig. 7-8

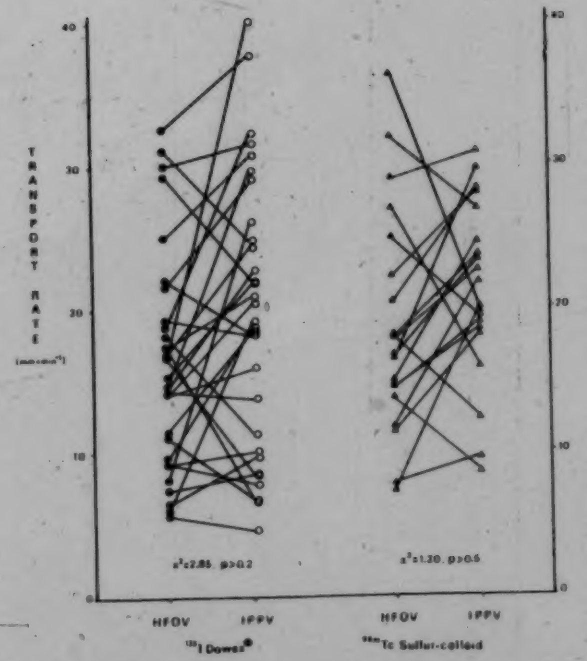

Figure 7-7: Tracheal transport rates of the two particle sizes during IPPV and SB. Figure 7-8: Tracheal transport rates of the two particle sizes during HFOV and IPPV. See text for details.

CHAPTER 8

COMPARISON OF THE EXPERIMENTAL BELLOWS OSCILLATOR WITH A COMMERCIALLY-AVAILABLE DIAPHRAGM OSCILLATOR

INTRODUCTION

All the HFOV experiments reported in this thesis were done with the metal-bellows oscillator described in Appendix I As there are no other reports in the literature describing the performance of this pump, the present set of experiments was undertaken to compare the effects of HFOV using the metal-bellows oscillator with a commercially-available diaphragm oscillator (Metrex model VSMV, Brampton, Ont.). Several hemodynamic, lung mechanic and gas exchange parameters were obtained from a group of dogs ventilated with the two HFOV pumps and with PEEP, at a $\bar{P}d$ of 10 cm H_2O.

METHODS

Seven mongrel dogs (7.5 ± 0.9 kg) were anesthetized with pentobarbital and intubated with a 9 mm i.d. cuffed ETT. While the animals were being ventilated with a model 607 Harvard respirator (at 15 bpm, V_T of 15 ml/kg and PEEP of 3 cm H_2O) procedures were performed and instrumentation was set-up (as described in Chapters 2 and 6) to obtain the following parameters: Pd, ΔTGV, $\overline{SAP}$, $\overline{PAP}$, PWP, LVEDP, dP/dt, PVR, PaO_2, $PaCO_2$, SaO_2, CaO_2, $P(A-a)O_2$ and O_2-Del. When instrumentation had been completed, the animals were placed in the body plethysmo-graph and the lid closed to allow the box temperature to equilibrate. The animals were ventilated at high frequency with either the diaphragm (DV) or the bellows (BV) oscillator (in random order) for 20 min. After this period, the above-described parameters were obtained, and ventilation with the alternate oscillator begun. After 20 min, another set of measurements were taken and a period of PEEP commenced. The experiment ended when the corresponding parameters were obtained after 20 min of PEEP.

HFOV was performed with both ventilators at 20 Hz. For BV the usual circuit was used (Chapter 3); the bias flow was set at 4 L/min and airway chamber pressure adjusted to induce a $\overline{P}d$ of 10 cm H_2O. For DV a circuit similar to the one described by Bohn et al. (1) was used. The LPF consisted of 150 cm of 9.5 mm i.d. Tygon tubing attached to 150 cm of Tygon 6.4 mm i.d. This tubing created a back pressure in the circuit of 0.47 cm H_2O when the bias flow was set at 30 L/min. When the LPF was clamped momentarily, the 20-Hz oscillations in Pbox induced by the V_T increased by less than 3%. Bias flow during DV was adjusted to induce a $\overline{P}d$ of 10 cm H_2O. During BV the gain of the Pbox amplifier was adjusted to obtain a full-scale deflection of the 20 Hz oscillation in Pbox (monitored on the oscilloscope of an Electronics for Medicine recorder model DR8). The volume delivered by the diaphragm pump was adjusted to induce a similar oscillation in Pbox. In the dogs assigned first to DV, a brief period of BV was performed to obtain the Pbox fluctuation necessary to adjust the V_T to be delivered by the diaphragm pump. Changes in FRC (ΔFRC) were obtained at the end of the 20-min ventilation periods by stopping the ventilator and leaving the ETT open to the atmosphere for 6--8 sec, and monitoring the volume change induced in the bell spirometer attached to the plethysmograph (Chapter 3).

The differences between the 3 ventilation periods were tested with a two-tailed paired t-test; significance was set at $p<0.05$.

RESULTS

Table 8-1 shows the average values of each parameter obtained during each ventilation period, as well as the statistical analysis. $\overline{P}d$ was similar during the 3 periods, as required by the protocol (Fig.8-1), however ΔTGV was lower during DV and statistical significance was only reached between DV and BV (Fig.8-2). There were no significant differences between hemodynamic parameters obtained during different ventilation periods. PaO_2 was significantly lower during DV (Fig.8-3), however $P(A-a)O_2$ was not different, (Fig.8-4). Even though there were no significant changes in $\dot{Q}$ (Fig.8-5) O_2Del was significantly lower during DV than during PEEP (Fig.8-6). The remaining parameters were statistically similar during the three types of ventilation.

DISCUSSION

The circuit used for DV can be compared to classical piston-pump systems (1), although minor variations in the waveform can be expected due to elasticity of the diaphragm (when viewed under a strobe light, "flutter" and uneven movement of the diaphragm could be observed). The LPF used in the present study was effective in "filtering out" the high-frequency component of ventilation without creating much back pressure from the bias flow. The combination of large (capacitance) and narrow (resistance) tubing retained over 97% of the high-frequency oscillation (97.9% in an in vivo test and 97.2% in vitro) inside the ventilatory circuit. The catheter used to deliver bias flow was very narrow (2 mm i.d.) and it is unlikely that much of the oscillation had escaped through it. Available information suggests that other LPF systems are less effective (2) but actual measurements were not performed, and reported data are only estimates. The present method used to match V_T and calculate the effectiveness of the LPF was based on relative changes in Pbox oscillation at the same frequency. Consequently the frequency response of the plethysmograph was not relevant.

It has been reported that classical HFOV systems are effective even at very low $\overline{P}aw$ (1); however, the BV requires higher distending pressure to achieve sufficient gas exchange (Appendix I). To compare the two pumps, $\overline{P}d$ was raised during DV to a level at which BV was always effective. This higher-than-necessary $\overline{P}d$ during DV might have induced an over-distension of the lungs and increase in "dead-space" ventilation with a tendency for CO_2 and $P(A-a)O_2$ to rise (the large SD probably prevented the difference from being significant). This might have also induced some hemodynamic impairment with a tendency for $\dot{Q}$ to be lower than during conventional ventilation (Fig.8-5), and causing a drop in O_2Del without a major change in CaO_2. If $\overline{P}d$ during DV had been lower a better gas exchange and hemodynamic function might be expected, as reported by other groups (1). The present results indicate that DV induces an increase in FRC similar to conventional ventilation (at the same $\overline{P}d$). In studies with a sick-lung model, Kolton et al. have reported higher FRC during DV than during conventional ventilation (3), but they measured $\overline{P}aw$ at a more proximal location, which might underestimate $\overline{P}alv$ (Chapter 9A).

The circuit used for BV delivers V_T into the airway through a narrow catheter (3 mm i.d.). It is conceivable that the higher velocity of the gas molecules coming out of the BV catheter enhances diffusion further than the DV thus explaining the tendency for better gas exchange with BV. It is difficult to explain the higher ΔFRC induced by BV. Although the higher energy of the gas molecules probably induced a larger airway pressure gradient during BV (Chapter 9A), $\overline{P}d$ was measured at a distal location and it seems to be a good estimate of $\overline{P}alv$ (Chapter 6). There is no reason to expect a better compliance of the lungs during BV, which might explain the higher FRC at the same

$\overline{P}d$. Also, a similar method of ΔFRC measurement was used in both instances and the presence of an artifact seems unlikely. The average difference in ΔFRC between BV and DV was 3.56 ml/kg; assuming linearity of the P/V relationship of the lungs and a compliance of 43.8 ml/cm H_2O (from Appendix IV) it can be estimated that $\overline{P}alv$ was around 0.6 cm H_2O higher during BV than DV. It is possible that this small pressure gradient between $\overline{P}alv$ and $\overline{P}d$ could not be detected by the method used in Chapter 6, and was responsible for the higher ΔFRC found during BV (which also could induce larger pressure gradients) in the present experiments.

The data of this study suggest a somewhat better performance of BV in terms of gas exchange, however $\overline{P}d$ was artificially raised during DV to match BV values. It is likely that at a lower $\overline{P}d$, gas exchange might have been similar or better during DV (BV is less effective at low $\overline{P}d$; see Appendix I). Available data suggest that in order to achieve similar gas exchange BV requires higher $\overline{P}d$ levels than DV and tends to impair cardiovascular function (Ref. 1 and Chapter 1).

In summary, BV and DV induced similar cardiovascular function at the same $\overline{P}d$ levels; gas exchange was slightly better and Δ FRC higher during BV.

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Table 8-1: Values obtained during each ventilation period, and statistical analysis of the comparisons between periods.

	BV	DV	PEEP	BV-DV	BV-PEEP	DV-PEEP
$\overline{P}$aw (cm H_2O)	10.0±0.32	10.0±0.34	10.0±0.10	NS	NS	NS
$\dot{Q}$ (ml/min)	868±133	929±251	992±198	NS	NS	NS
$\overline{SAP}$ (mm Hg)	109±21.1	107±15.5	107±16.7	NS	NS	NS
$\overline{PAP}$ (mm Hg)	19.7±3.33	20.7±3.23	19.3±4.10	NS	NS	NS
PWP (mm Hg)	5.77±1.14	6.43±1.18	5.67±1.33	NS	NS	NS
LVEDP (mm Hg)	5.04±1.04	5.49±0.99	4.71±1.21	NS	NS	NS
PWP-LVEDP (mm Hg)	0.71±5.70	0.93±0.79	0.90±0.34	NS	NS	NS
dP/dt (mm Hg/sec)	10.8±2.42	10.3±2.78	10.8±2.52	NS	NS	NS
ΔFRC (ml/kg)	25.1±5.09	21.5±4.25	25.5±5.53	*	NS	NS
PVR (dyn x sec/cm^5)	1324±405	1293±443	1177±517	NS	NS	NS
PaO_2 (torr)	90.8±9.64	82.1±10.1	90.6±4.43	*	NS	*
$PaCO_2$ (torr)	34.6±7.34	38.0±5.96	34.2±4.58	NS	NS	NS
SaO_2 (%)	92.4±2.92	89.8±3.86	93.0±1.01	NS	NS	NS
CaO_2 (ml/100)	19.3±1.34	18.7±1.56	19.4±1.46	NS	NS	NS
$P(A-a)O_2$ (torr)	3.03±2.03	7.60±5.34	3.65±2.6	NS	NS	NS
O_2Del	167±25.8	175±54.1	194±52.1	NS	NS	*

Values are mean ± SD. NS: $p>0.05$; *: $p<0.05$.

BV: bellows vent.; DV: diaphragm vent.; PEEP: conventional vent.

Fig. 8-1

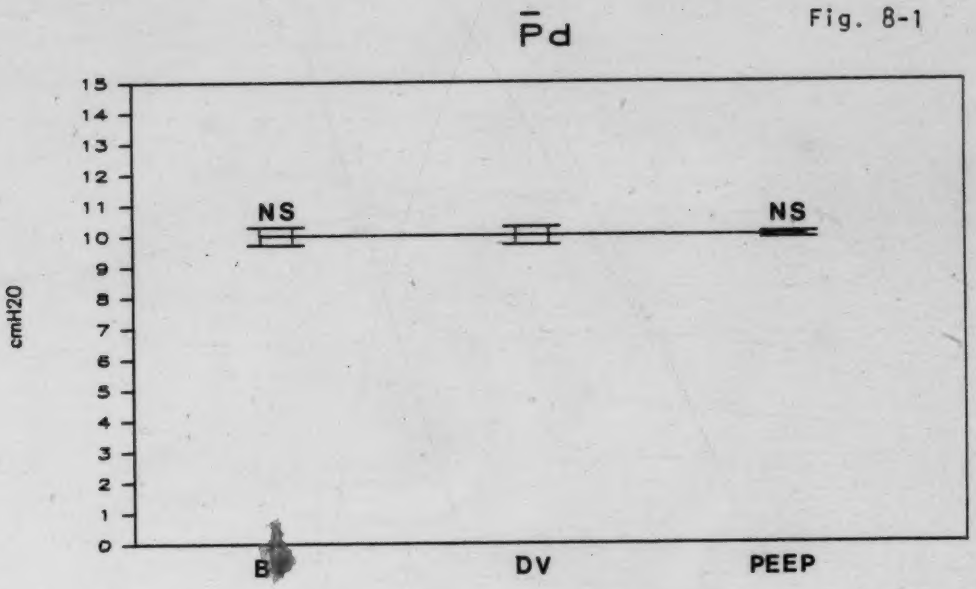
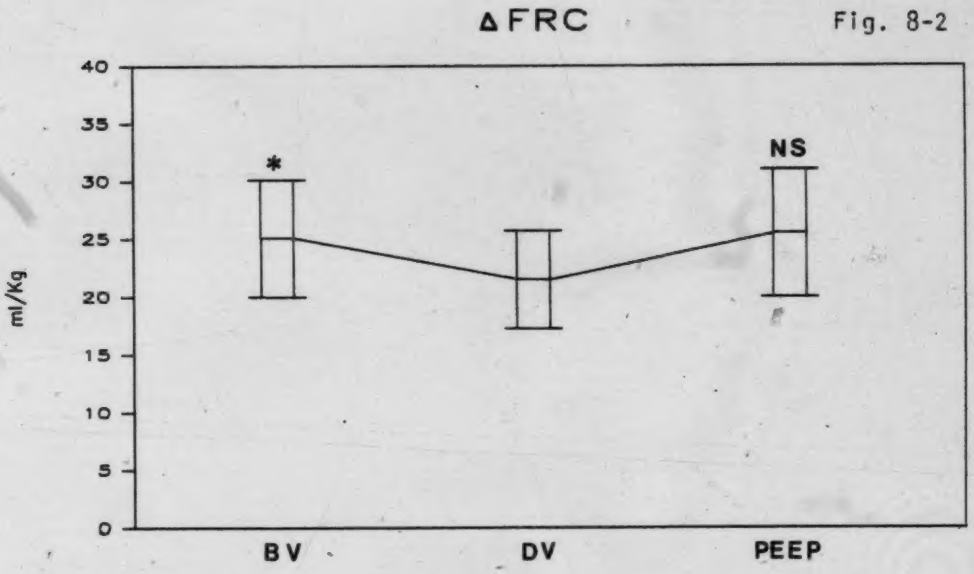
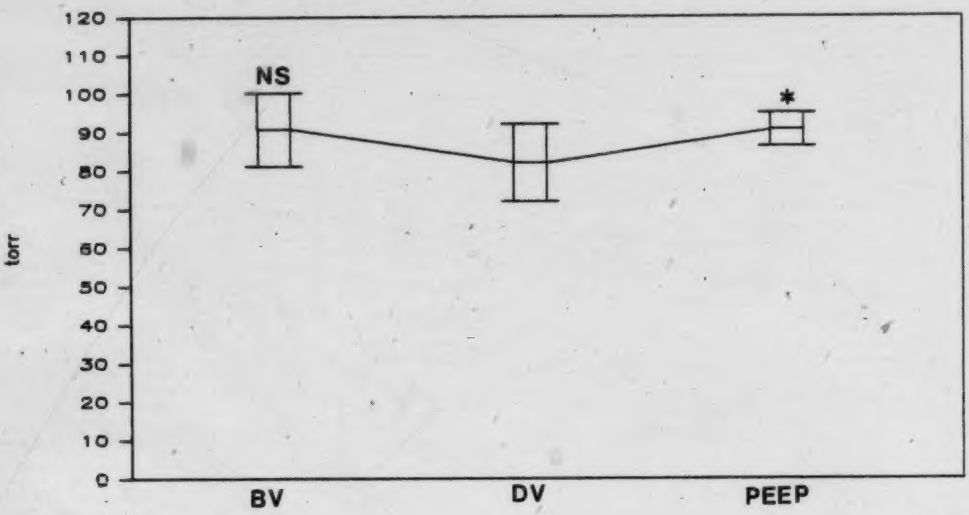


Fig. 8-2



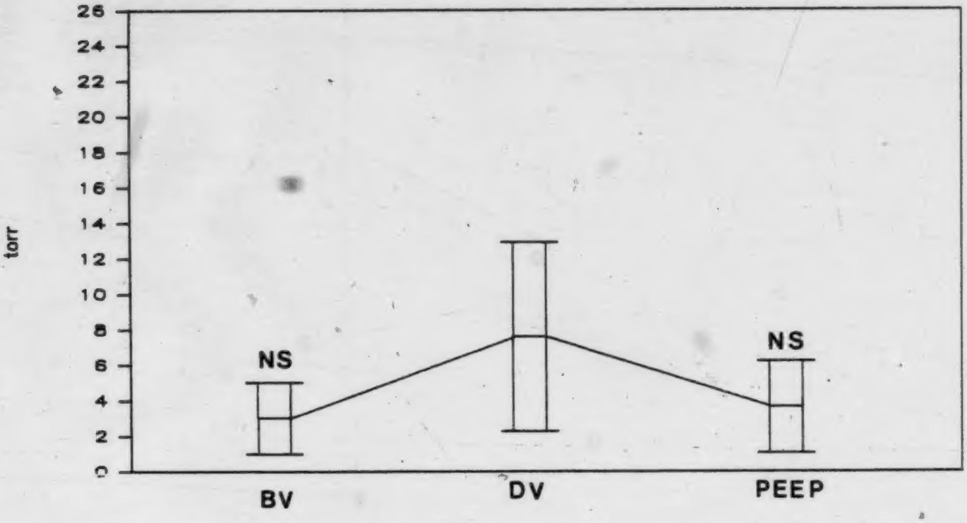
Figures 8-1 and 8-2: Average mean distal airway pressure (top) and change in functional residual capacity (bottom) changes (±SD) in the studies comparing the diaphragm oscillator with the bellows pump and conventional ventilation. NS, $p>0.05$; $*0.05>p>0.01$.

Fig. 8-3



PaO_2

Fig. 8-4



P(A−a)O2

Figures 8-3 and 8-4: Average arterial PO_2 (top) and alveolo-arterial O_2 gradient (bottom) changes (±SD) in the studies comparing the diaphragm oscillator with the bellows pump and conventional ventilation. Symbols as in fig 8-1.

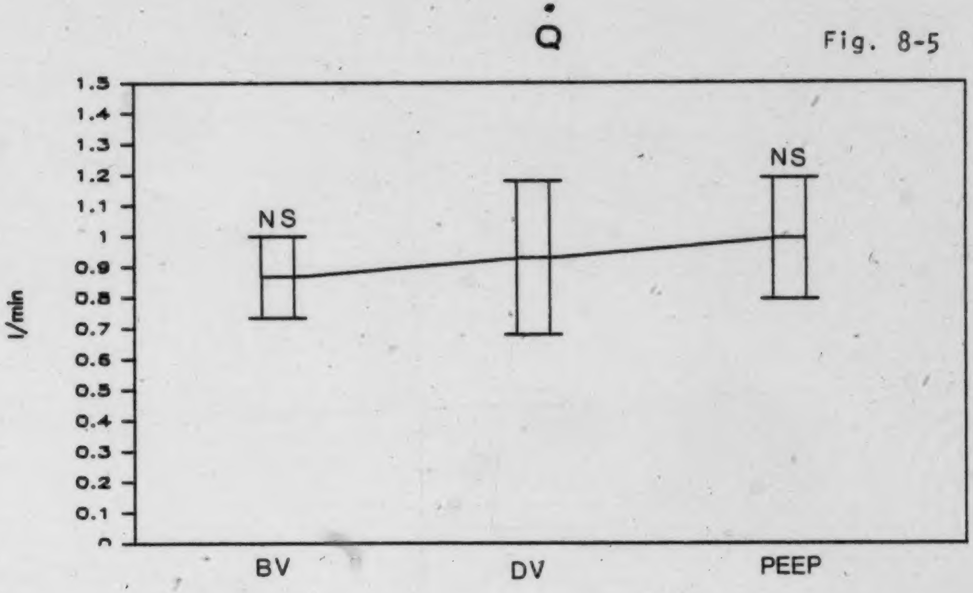


Fig. 8-5

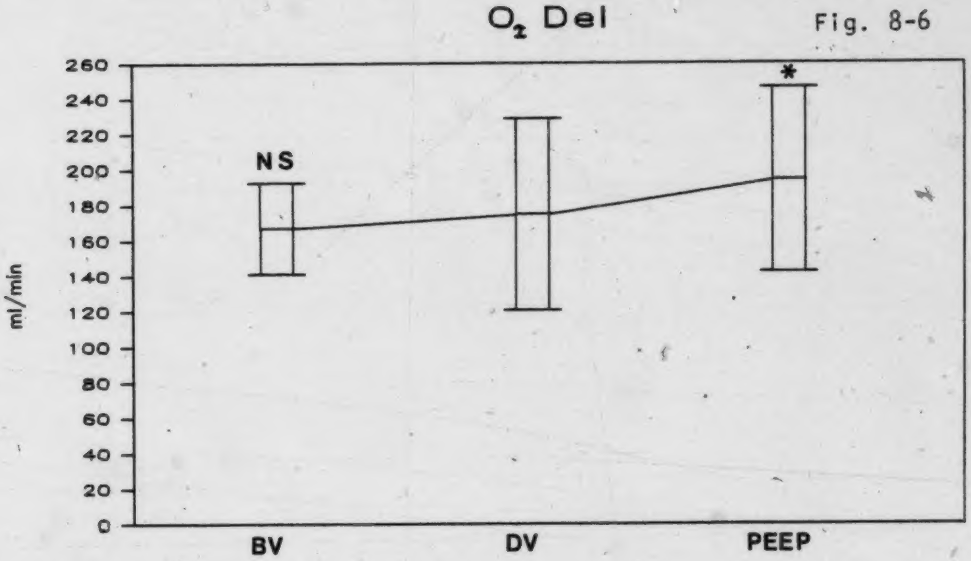


Fig. 8-6

Figures 8-5 and 8-6: Average cardiac output (top) and O_2 delivery (bottom) changes (±SD) in the studies comparing the diaphragm oscillator with the bellows pump and conventional ventilation. Symbols as in Fig. 8-1.

CHAPTER 9

CHAPTER 9A

Chapter 9A: AIRWAY PRESSURE GRADIENTS CREATED BY HIGH-FREQUENCY OSCILLATORY VENTILATION

INTRODUCTION

During high frequency oscillatory ventilation (HFOV), gas exchange is achieved with low tidal volumes but very high respiratory rates (3). This mode of ventilation causes gas to flow at high velocity and consequently gas molecules acquire considerable kinetic energy. As pressure waves travel down the airways during HFOV, energy gradients (i.e. changes in kinetic and potential energy with distance) may be created that are quite different from what would be expected during conventional ventilation (4,16). In the studies of lung mechanics during HFOV (Chapter 2) a consistent discrepancy was observed between proximal mean airway pressure at a given resting lung volume, and the mean alveolar pressure that could be predicted from static pressure/volume curves of the lungs. The data suggested that pressure increased from the proximal to distal airways. In the present study, catheters were threaded down the airways of intact and isolated dog lungs and this pressure gradient was confirmed. To rule out artifacts due to the measuring catheter, a retrograde catheter technique (9) was also used to quantify the pressure gradients in the isolated lungs.

MATERIALS AND METHODS

In vivo experiments: Eight mongrel dogs (7.3 ± 0.8 Kg) were anesthetized with i.v. pentobarbital (30 mg/kg) and intubated with a 9 mm i.d. cuffed endotracheal tube. Cuff pressure was monitored throughout the experiment and kept above 40 cm H_2O. The animals were ventilated with the oscillator circuit described in Chapter 1 at 20 Hz and 4 L/min of bias flow. One animal (#3) was also ventilated at 15,25 and 30 Hz.

Proximal airway pressure was measured with a 3 mm i.d. rigid plastic tube (introduced 2.5 mm into the lumen of the ETT) and a Validyne differential pressure transducer (model MP45). The catheter-transducer system was found to have a flat frequency response to at least 50 Hz. Mean airway pressure ($\overline{Paw}$) was obtained by electronic averaging. Pressure gradients down the airway were measured with a Polyethylene catheter (1.27 mm o.d., 0.86 mm i.d.). The proximal end of the catheter was attached to a P300 Validyne differential pressure transducer, and the distal tip was occluded but had six side holes drilled in the last 15 mm of it. The catheter was marked every 25 mm to aid in positioning the tip in the airway. An airtight opening in the ETT wall allowed threading the catheter down the airway to measure mean distal airway pressure ($\overline{Pd}$) at various distances, starting 5 cm from the ETT proximal end Introduction of the catheter increased $\overline{Paw}$ by less than 0.2 cm H_2O, and this did not change with advancement of the catheter.

The electronically-averaged outputs of both transducers were displayed on digital voltmeters (Hewlett Packard model 3430A for $\overline{Paw}$ and Gould model 13-4611-10 for $\overline{Pd}$) to facilitate rapid and precise readings. The output of the Pd amplifier was also displayed on a strip chart recorder (Gould model 2600S) to assess when the catheter tip had been wedged in a small airway (the 20-Hz pressure oscillations ceased). Only $\overline{Pd}$ readings prior to wedging were used. In preliminary trials it was found that the proximal - distal $\overline{Pd}$ gradient ($\overline{Pd}$ profile) was not significantly affected when a larger diameter catheter was used (1.90 mm o.d., 1.41 mm i.d.), but obviously, wedging occurred more proximally than with the smaller-diameter catheter.

A total of 24 $\overline{Pd}$ profiles (with individual measurements taken at 25 or 50 mm intervals) were obtained from the 8 dogs (3 dogs had 2 profiles each, 4 had 3 profiles and one had 6). One of the dogs (#3) had also pressure profiles obtained during ventilation at 15, 25 and 30 Hz. In the first three dogs, simultaneous readings of $\overline{Paw}$ were taken at each $\overline{Pd}$ level, to correct for any effects of $\overline{Paw}$ fluctuations on $\overline{Pd}$ values, but this was found to be unnecessary and was not done in the other five dogs. Oscillation induced whipping of the catheter tip in the first few centimeters of the ETT, and this created an artifact that caused fluctuating $\overline{Pd}$ readings. Consequently, only values obtained after the first 5 cm are presented.

In vitro experiments: Two normal freshly excised dog lung lobes (right lower lobe of two animals weighing 22 and 26 Kg, respectively) were studied. The main bronchus was attached to a 9-mm ETT and the lobes oscillated with the ventilator as previously described; similar transducers and catheters were used for $\overline{Paw}$ and $\overline{Pd}$ measurements. $\overline{Paw}$ was maintained close to 9.75 cm H_2O. Two sets of $\overline{Pd}$ profiles were obtained on each lobe as described above. In addition, four $\overline{Pd}$ profiles were obtained on each lobe by a retrograde catheter technique similar to the one described by Macklem and Mead (9). The procedure was as follows: a thin metal wire was pushed down the airway until its end pierced the pleura. A catheter similar to the smaller one previously described for the $\overline{P}d$ measurements, was passed over the wire until it exited through the pleural surface, and the wire was then withdrawn. The distal end of the catheter was occluded and had six lateral holes. No funnel-like shape, as described by Macklem and Mead (9), was used because it was felt that such a design may not accurately reflect mean values from a rapidly- alternating pressure wave. The open end of the catheter was attached to the P300 transducer and the catheter pulled through the pleura to position the distal tip at different levels in the airways. Readings of $\overline{P}d$ were taken until the pressure oscillations ceased, due to occlusion of the side holes by the distal airway wall. At this point, the catheter was advanced proximally to the ETT level, and the readings repeated. A total of 8 sets of $\overline{P}d$ measurements were obtained, four in each lobe; on 3 occasions two profiles were obtained with the catheter passing through the same pleural opening.

Statistical analysis of the data was performed with a paired Student's t-test to compare $\overline{P}d$ obtained at different levels. The significance level was established at $p<0.05$. Results are expressed as mean ± standard deviation.

RESULTS

In vivo experiments: $\overline{P}d$ profiles obtained from each of the 8 dogs are shown in Fig.9A-1. $\overline{P}d$ remained constant until the catheter tip reached the distal end of the ETT. Beyond this point there was a gradual rise in $\overline{P}d$, more pronounced in the first few centimeters, which continued until the tip was wedged. Fig.9A-2 shows average values for $\overline{P}d$ obtained at three levels: in the ETT, 5 cm distal to the ETT tip, and the last measurement before wedging. The $\overline{Pd}$ obtained inside the ETT averaged 9.75 ± 2.20 cm H_2O and increased by 1.35 ± 0.61 cm H_2O at 5 cm beyond the ETT tip and by 2.18 ± 0.71 cm H_2O before wedging (ranging from 1.00 to 3.36 cm H_2O). Both were significantly higher than average ETT $\overline{Pd}$ ($p<0.001$). The average difference between $\overline{Pd}$ at 5 cm from the endotube tip and pre-wedging $\overline{Pd}$ was 0.94 ± 0.42 cm H_2O, which was also statistically significant ($p<0.001$). The average distance from the ETT tip to the level of the final $\overline{Pd}$ (taken just before wedging occurred) was 14.60 ± 6.41 cm. Fig.9A-3 shows the pressure profiles obtained at different frequencies in dog #3. A gradient in $\overline{Pd}$ was observed at all frequencies, with a tendency to be larger as frequency increased.

In vitro experiments: The $\overline{Pd}$ data obtained from the isolated lobes are shown in Fig.9A-4. The $\overline{Pd}$ profile obtained with both catheter methods were similar to those found in vivo. The $\overline{Pd}$ 5 cm beyond the ETT tip was 1.47 ± 0.60 cm H_2O higher, and the final $\overline{Pd}$ 2.32 ± 0.75 cm H_2O higher than average ETT $\overline{Pd}$; both differences were statistically significant ($p<0.001$). The average difference between $\overline{Pd}$ measured 5 cm beyond the ETT tip and pre-wedging $\overline{Pd}$ was 0.84 ± 0.69 cm H_2O, which was also significant ($p<0.025$).

DISCUSSION

Recent work published by Thompson et al. indicated that one of the most important variables in determining oxygenation during HFOV is $\overline{Paw}$ (17). Airway pressure also has important effects on the cardiovascular system (14). However different groups use different techniques to measure $\overline{Paw}$ during HFOV, and $\overline{Paw}$ is measured at different sites: proximal end of the ETT (5,6,10) tip of the ETT (17), 3 cm (5) or 5 cm

(15) distal to the ETT tip, or beyond the carina (10). As the present results show that $\overline{P}aw$ varies with the measurement site, comparison of the $\overline{P}aw$ values reported by different groups would be questionable. Other authors have observed the presence of these pressure gradients (4,10,12,13,16).

It was found that mean pressure inside the ETT is quite constant, but there is a sharp increase in the first 5 cm after the ETT tip, followed by a more gradual increase down to the small airway level. The average pressure gradient between the ETT and the wedged position in small airways was usually over 2 cm H_2O, and sometimes this gradient exceeded 3 cm H_2O. When HFOV frequency vas varied in one of the dogs (#3), there was a small change in the absolute value of $\overline{P}d$ and in the magnitude of the pressure change (Fig.9A-3) but the shape of the pressure profiles was quite consistent. This suggests that the presence of the pressure gradients was not specific to a HFOV frequency of 20 Hz. In the present experiments, wedging occurred in airways of approximately 1.2 mm (o.d. of the measuring catheter), which corresponds to the 5--7th generation (7). The studies reported in Chapter 6 suggest that, during HFOV, mean alveolar pressure is close to the $\overline{P}d$ measured in the small airways. Thus it seems that the most appropriate place to monitor $\overline{P}aw$ during HFOV is in distal airways. However, narrow catheters used to obtain$\overline{P}d$ often become occluded by secretions and have to be removed for cleanup. It might be more practical to obtain a pressure profile for a given frequency-volume combination, and use it to correct $\overline{P}aw$ values measured in a proximal position (assuming that the profiles remain constant).

There are several reasons which indicate that the pressure gradients found were not due to an artifact induced by the measuring catheter. When a larger catheter was used (2.84 mm^2 crossectional area vs 1.26 mm^2), the gradients obtained were similar, even though the relationship of crossectional areas between the airway and catheter was quite different. In distal airways the pressure gradient was small although the airway/catheter crossectional area ratio was changing rapidly with distance; the overall gradients were also not appreciably affected by catheter size. Using the retrograde catheter technique, the possible artifacts due to the presence of the measuring catheter in proximal airways were minimzed, but the pressure gradients obtained were similar to those obtained with the forward catheter technique.

The pressure increase from proximal to distal airways can be explained in part by the Bernoulli's priniciple: "pressure plus the total mechanical energy per unit volume is the same everywhere in a flow tube" (8). In the respiratory tree, the total crossectional area of the airways increases as we get closer to the alveoli (11), or in the transition from the ETT to the trachea (134% increase in area calculated from Ref. 7); therefore, the gas velocity and consequently its mechanical energy decrease. According to Bernoulli's principle, the pressure ($\overline{P}d$) must increase as mechanical energy decreases (8). Breen et al., using their own data, calculated a pressure gradient of 0.55 cm H_2O; using a different approach, the calculated gradient was 1.45 cm H_2O (4). Some authors have suggested that other "non-Bernoulli" factors are also involved (16), which could include energy changes due to frictional and inertial phenomena, and an air-trapping effect during expiration.

In conclusion, the present experiments show that during HFOV there is a pressure gradient down the respiratory tree that causes the mean distal airway pressure to be higher than the pressure measured at the airway opening. The presence of this gradient must be taken into account whenever the effect of $\overline{P}aw$ on oxygenation, cardiovascular function, lung volumes, etc., is studied during HFOV. By positionning the tip of the measuring catheter just proximal to the wedged location, an approximation of alveolar pressure could be obtained.

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Fig. 9A-1

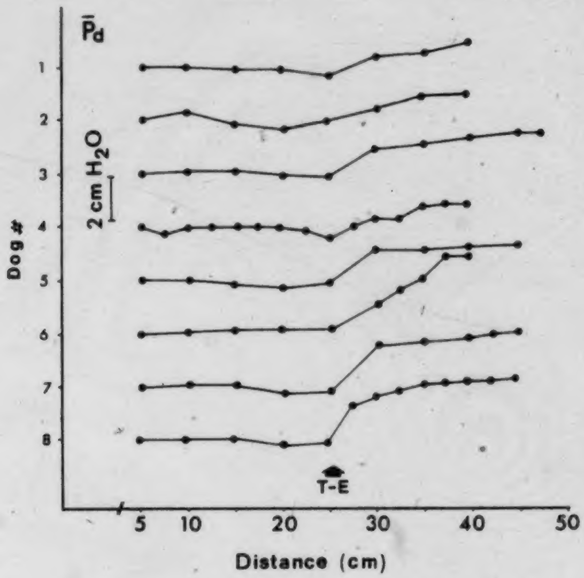

Fig. 9A-2

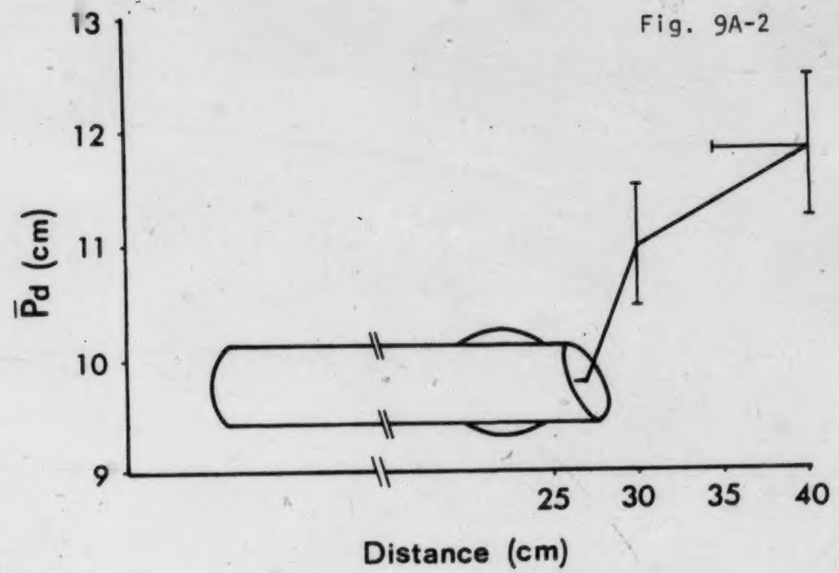

Fig.9A-1: Mean airway pressure ($\bar{P}d$) profiles during HFOV from eight dogs. T-E, tip of the endotracheal tube. Fig.9A-2: Average mean airway pressures ($\bar{P}d$) at different levels of the respiratory tree: endotracheal tube, 5 cm beyond the tube tip and pre-wedging position. Bars represent ± SD.

Fig. 9A-3

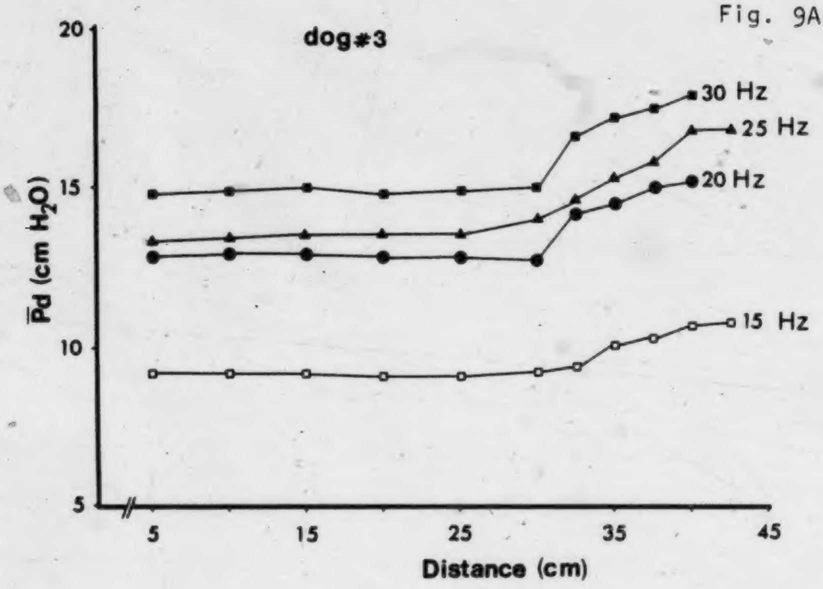

Fig. 9A-4

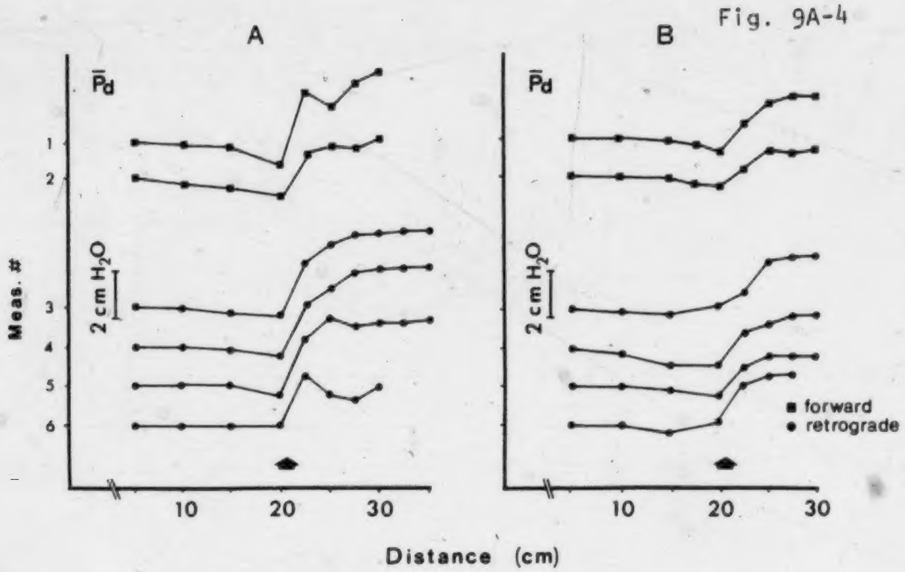

Fig.9A-3: Pressure profiles obtained in dog #3 at different HFOV frequencies. Fig.9A-4: Mean airway pressure (P̄d) profiles during HFOV in two lung lobes (A and B) using forward (measurements 1 and 2) and retrograde (measurements 3 to 6) techniques. Arrow: endotracheal tube tip

Capter 9B: CARBON DIOXIDE GRADIENTS IN THE RESPIRATORY TREE DURING HFOV

INTRODUCTION

During HFOV gas exchange can be accomplished with a V_T smaller than V_{Dan}, probably through the combined effects of convection and enhanced diffusion (see Introduction). It was postulated that during HFOV, the enhanced diffusion would tend to create a CO_2 concentration gradient down the airways. To investigate this possibility, gases were sampled and analyzed for CO_2 concentration at different levels in the respiratory tree of two dogs ventilated with HFOV.

METHODS

Two mongrel dogs (weight 6.2 and 8.9 kg) were anesthetized with pentobarbital, intubated and ventilated with the standard HFOV circuit (Chapter 1) at 25 Hz and 4 L/min of bias flow of air. A 50-cm long Polyethylene catheter (0.9 mm i.d.) was connected to a Godart capnograph and threaded down the airway. Readings of CO_2 concentration were taken at different levels down the respiratory tree, until the catheter was wedged in a small airway. The capnograph readings were taken in each position after an equilibration period of at least 3 s (the 95% response time of the capnograph-catheter system was 2.6 s). The capnograph had been previously calibrated (with the catheter connected) with 5% CO_2.

RESULTS

Figure 9B-1 shows the CO_2 concentrations obtained at different levels of the respiratory tree in the two dogs. The open symbols correspond to the large dog and the closed symbols to the smaller one. There was a slight increase in CO_2 down the ETT, after which the concentration increased much faster, with the steepest rise in distal portions of the airways.

DISCUSSION

This study confirms the presence of a CO_2 gradient down the airways, induced by HFOV, which has been suggested by other authors (see Introduction). The higher CO_2 concentration in the larger dog, may have been related to a higher CO_2 production. In the present experiments, simultaneous values of $PaCO_2$ were not available. It is likely that, if it were technically possible to measure it, the CO_2 concentration would continue to increase if samples were taken in smaller airways until the alveolar level had been reached. At this level, the CO_2 concentration should give a value close to $PaCO_2$.

The system used to measure CO_2 in the present experiments had a very slow frequency response compared to the HFOV rate. Thus the values obtained represented an average reading of a sample obtained over several seconds. It is conceivable that if the measurements had been obtained with a system having an extremely high frequency response (much faster than the HFOV rate) CO_2 concentration would likely fluctuate with the ventilatory cycle in the airway generations where bulk transport exists. Although mass spectrometers have an appropriate frequency response, the sampling catheters slow this response down to an impractical level.

Fig. 9B-1

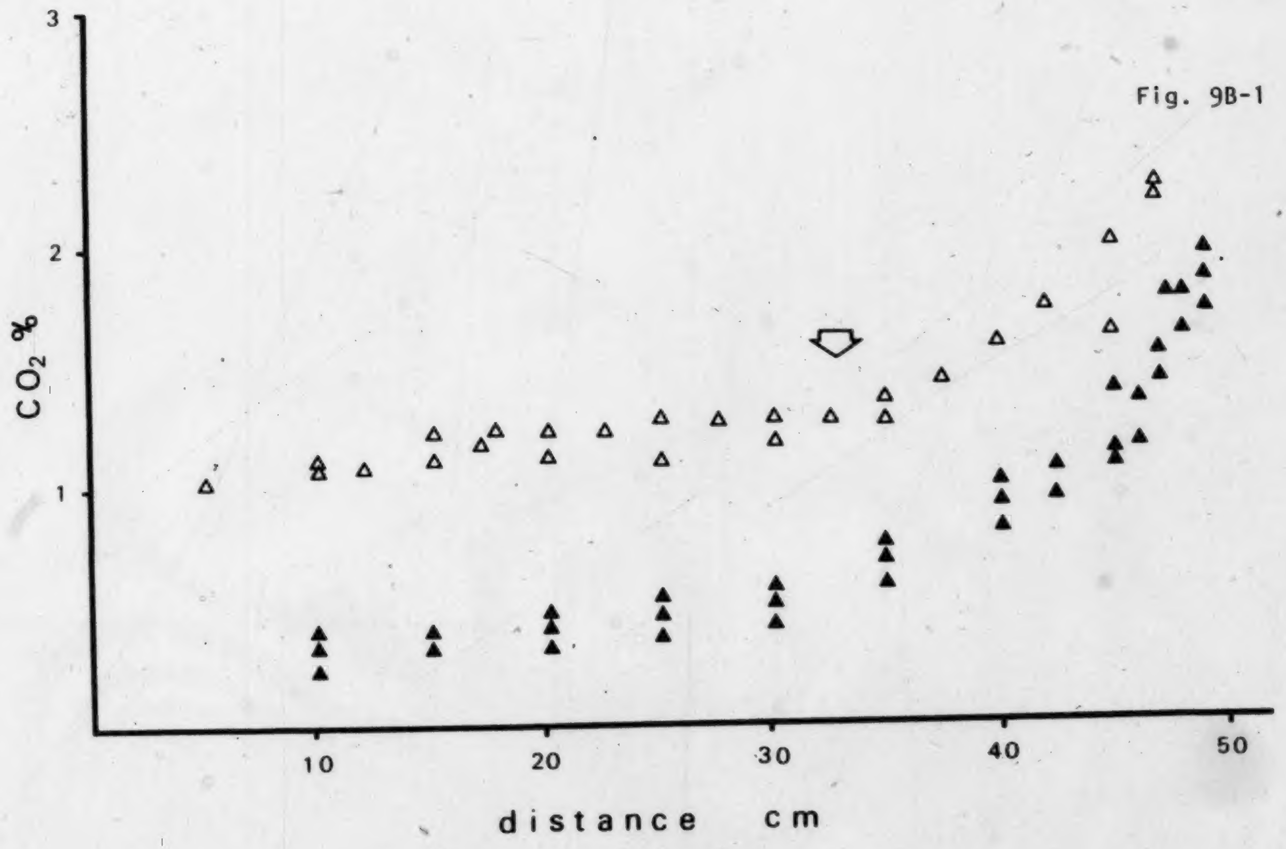

Figure 9B-1: CO$_2$ concentration at different points down the airways of two dogs. Open triangles, larger animal; arrow, tip of the endotracheal tube.

Chapter 9C: ROLE OF PROSTAGLANDINS IN THE PULMONARY VASCULAR RESPONSE TO HFOV

INTRODUCTION

In previous studies(Chapters 1,2,4) HFOV was found to induce a gradual increase in pulmonary artery pressure in dogs, that was established in a period of less than a minute. Since this could not be explained by blood gas changes, it was thought that the pulmonary hypertension could have been due to a gradual increase in lung volume (or intrathoracic pressure) or been mediated through a vaso-constrictor substance liberated in the lungs by the vibratory stimulus of HFOV. It has been known for many years that mechanical stimulation (agitation, stirring) is an excellent way to liberate PG's from the lung (8,9), so it was speculated that PG's could be involved in the increase in pulmonary artery pressure induced by HFOV.

This chapter describes the effects of Indomethacin, a PG-synthesis blocker, on the pulmonary artery pressor response to HFOV.

MATERIALS AND METHODS

Seven mongrel dogs (8.0 ± 1.3 kg) were anesthetized with intravenous pentobarbital (30 mg/kg), intubated with a cuffed endotracheal tube (9 mm i.d.) and ventilated with IPPV at 15 breaths/min and a tidal volume of 15 ml/kg using a Harvard respirator (model 607). A femoral artery catheter was used to obtain samples for blood gas analysis (Instrumentation Laboratory model 813) and to monitor systemic blood pressure (Statham transducer model P23Db). A femoral vein catheter was used to maintain anesthesia with pentobarbital (3—6 mg/kg every hour) and infuse 2.3% glucose in 0.3% saline at 4 ml/kg/h. Pulmonary artery pressure was measured with a flow directed catheter (Edwards Laboratories model 93A-301-7F) connected to a calibrated pressure transducer (Statham Model P23Db). The transducers were zeroed at the level of the right atrium. Systemic and pulmonary artery pressure tracings were displayed on a strip chart recorder (Gould model 2600S).

The dogs could also be ventilated with the high frequency pump with the 290-ml airway pressure chamber in place (Fig.9C-1), which was flushed continuously by an air flow of 15 L/min. To monitor $\overline{P}aw$, a rigid plastic catheter (3 mm i.d.) was introduced 2.5 mm into the endotracheal tube wall, 40 mm distal to the tips of the ventilation catheters, and connected to an MP45 Validyne differential pressure transducer.

Experimental Protocol: To supress PG production, 15 mg/kg of Indomethacin (IDM) were infused into the dog's femoral vein catheter over a period of 4 min (7). The drug was injected as a freshly prepared solution of 15 mg/ml of IDM (Sigma Laboratories) with 15 mg/ml sodium bicarbonate in water. The IDM infusion produced minor and reversible fluctuations in pulmonary and systemic arterial pressures in some dogs. Ten minutes before and 60 min after the IDM infusion, the dogs were ventilated with the oscillator (20 Hz and 4 L/min) for 5 min and

PAP recorded.

Data Analysis; Baseline PAP was obtained during a 10-15 s period of apnea before starting HFOV. As electronic averaging would tend to blunt time-related changes, $\overline{PAP}$ was calculated from the tracings as: pulmonary diastolic pressure plus one third the pulse pressure. Increases in $\overline{PAP}$ induced by HFOV were plotted against time, and found to fit an exponential relationship. During both apnea (baseline) and 1--2 min after starting HFOV (plateau), six successive $\overline{PAP}$ values were obtained from the recording and averaged. The slope of the exponential rise in $\overline{PAP}$ was calculated by the least squares method (12) taking baseline $\overline{PAP}$ as 100% and plateau $\overline{PAP}$ during HFOV as 0%. The first 3 to 5 beats after starting of HFOV were not used for the calculation of the curve slope since they fluctuated irregularly. One minute after the start of HFOV, an arterial blood gas sample was taken and analyzed.

A two-tailed Student's paired t-test was used to compare the following groups of data: 1) slope of the exponential rise in PAP induced by HFOV before and after IDM infusion; 2) baseline $\overline{PAP}$ before and after IDM; 3) plateau $\overline{PAP}$ during HFOV before and after IDM, 4) percent rise in $\overline{PAP}$ above baseline before and after IDM, and 5) $PaCO_2$ and PaO_2 during IPPV before the IDM administration and one minute after starting the two HFOV runs (one before and one after IDM). Data are presented as mean ± SD; significance was set at $p<0.05$.

RESULTS

A representative tracing of PAP changes induced by HFOV, is reproduced in Fig.9C-2. Table 9C-I shows the statistical analysis of the $\overline{PAP}$ data. No statistically-significant differences were found between the following PAP-derived parameters, measured before and one hour after the infusion of IDM: 1) Baseline $\overline{PAP}$ (apnea); 2) plateau $\overline{PAP}$ during HFOV; 3) percent change in $\overline{PAP}$; and 4) slope of the exponential increase in $\overline{PAP}$, induced by HFOV. All the correlation coefficients of the exponential curves were significant ($p<0.001$).

Baseline $PaCO_2$ during IPPV (before IDM) was 33.1 ± 3.5 and PaO_2 91.8 ± 10.0. Mean $PaCO_2$ during HFOV before IDM was 33.1 ± 5.1 mm Hg and after IDM 32.3 ± 4.9 mm Hg. Mean PaO_2 during HFOV before IDM was 89.9 ± 8.8 mm Hg and after IDM 89.7 ± 4.3 mm Hg. These values for $PaCO_2$ or PaO_2 were not different from the baseline. The values of $\bar{P}$aw during HFOV before and one hour after IDM were also similar (9.9 ± 0.3 cm H_2O and 10.0 ± 0.4 cm H_2O respectively).

DISCUSSION

During HFOV, respiratory rates of 5 to 30 Hz are needed to achieve gas exchange (1). The effects on the organism of mechanical stimulation at this frequency range, must be characterized in order to establish the safety of this new approach to artificial ventilation. One of the possible side effects of HFOV could be to induce the secretion of PG's, since it is known that mechanical stimulation can trigger PG release from the lung (8,9). Recent studies suggest that PG-related substances may be involved in the pathophysiology of the respiratory distress syndrome (10), so the HFOV-induced release of PG's could be deleterious to already critically-ill patients. There are no studies on the role of PG's during HFOV in normal lungs.

In previous studies(Chapters 1,2,4) it was found that HFOV induced a significant increase in $\overline{PAP}$ and pulmonary vascular resistances. As in these studies, blood gas parameters did not change significantly during HFOV, two different mechanisms could be postulated for this pulmonary pressor response: a mediator release (3) or distension and compression of pulmonary capillaries induced by increased lung volumes and alveolar pressures (13).

As mentioned earlier, PG's are released by mechanical stimulation of the lung, and we speculated that they might be responsible for the observed pulmonary hypertension. Several PG's synthetized in the lung have pulmonary vasocontrictor activity; they include: PGF2α, PGF1α, PGE2, PGA2 and PGD2 (5). Also a group of PG-related substances, the thromboxanes, are potent pulmonary vasoconstrictors synthetized in the lung (5). According to Needleman, one of the criteria to involve PG's in the mediation of biological processes is: "the abolition of the synthesis of PG's should abolish the physiological action of the stimulus" (6). Consequently, in the present study it was speculated that if PG's were involved in the pulmonary hypertensive response to HFOV, the blockade of their synthesis by IDM would decrease or inhibit this response. Indomethacin was used at a dose high enough to abolish PG (and thromboxane) production (11); however, this did not modify significantly the pulmonary vasopressor response to HFOV, as assessed by the magnitude (percent change) and time course (slope of the exponential rise) of the $\overline{PAP}$ changes. Both baseline (apnea) and plateau (HFOV) $\overline{PAP}$ values were similar before and after IDM, indicating that IDM did not modify the status of the pulmonary circulation. In previous experiments (Chapter 1) it was found that the increase in $\overline{PAP}$ during

HFOV was associated with a decrease in cardiac output, and that pulmonary vascular resistance (PVR) was increased. Consequently, it seems unlikely that, in the present study, an increased cardiac output was responsible for the increased $\overline{\text{PAP}}$ during HFOV leaving PVR unchanged. The changes in pulmonary artery "wedge" pressure observed in those experiments were much smaller than $\overline{\text{PAP}}$ changes, thus ruling out an increase in left atrial pressure as responsible for the increase in $\overline{\text{PAP}}$. The findings reported in Chapter 3 also support this theory.

The present experiments indicate that the rise in $\overline{\text{PAP}}$ (and PVR) was not mediated through PG (or thromboxane) release. However, this does not rule out the possibility of HFOV-induced PG secretion by the lung: a balanced amount of vasoconstrictor and vasodilator PG's could be liberated; or PG's could have been metabolized before reaching the vascular receptor.

The role of other mediators with pulmonary vasoconstrictor activity, like catecholamines, histamine, angiotensin, serotonin (2) or leukotrienes, was not investigated in the present study. However, in previous experiments (Chapter 1) it was found that heart rate did not increase during HFOV, suggesting that a release of mediators with chrono-tropic activity: catecholamines, serotonin and histamine (4), did not take place. A remote possibility exists that the mechanisms of activation of the renin-angiotensin system (4) had been triggered by HFOV. However, in order to be able to exclude the role of any of these mediators, further experiments using either specific blockers and/or assays will be needed.

If known vasoactive substances are not involved in the pulmonary artery pressor response to HFOV, then it seems likely that the increased lung volume and/or alveolar pressure have a major effect, as observed during conventional ventilation (14). In previous experiments (Chapter 2) it was found that HFOV induced a substantial rise in mean airway pressure and FRC, and that 15 to 30 seconds were required to obtain an almost complete increase in lung volume after starting HFOV. The time course of the present $\overline{\text{PAP}}$ response was somewhat slower, and this could be related to the time taken for a widespread alveolar recruitment to become established.

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TABLE 9C-1: Effect of Indomethacin (IDM) on the $\overline{PAP}$ response to HFOV

	Before IDM	After IDM	
Baseline PAP (mm Hg)	14.5 ± 2.5	14.1 ± 4.8	NS
Plateau $\overline{PAP}$ (mm Hg)	18.5 ± 3.2	18.1 ± 5.4	NS
Change in $\overline{PAP}$ (%)	27.2 ± 5.6	30.0 ± 7.2	NS
Slope of $\overline{PAP}$ rise (arbitrary units)	0.138 ± 0.051	0.144 ± 0.048	NS

Values expressed as mean ± SD; n=7. NS = difference not statistically significant.

Fig. 9C-1

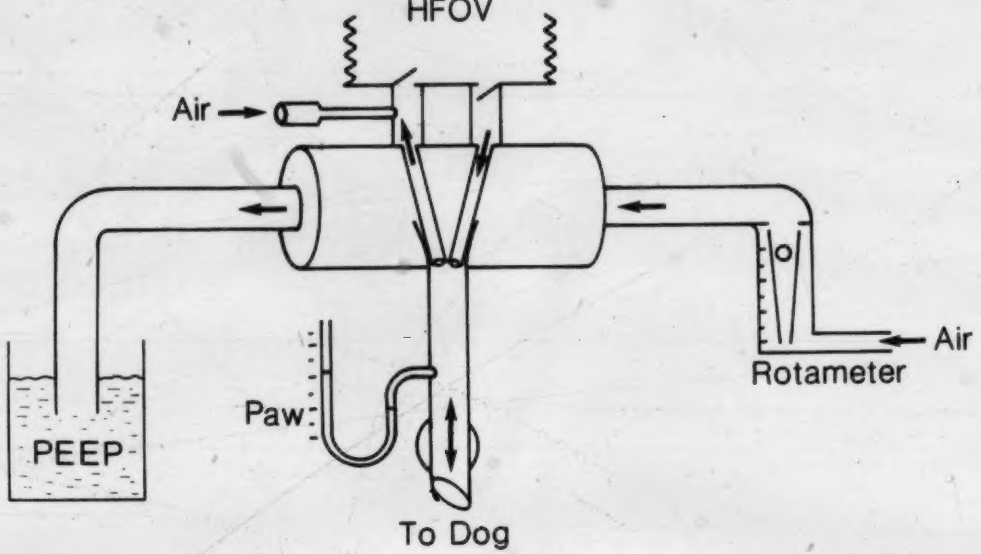

Fig. 9C-2

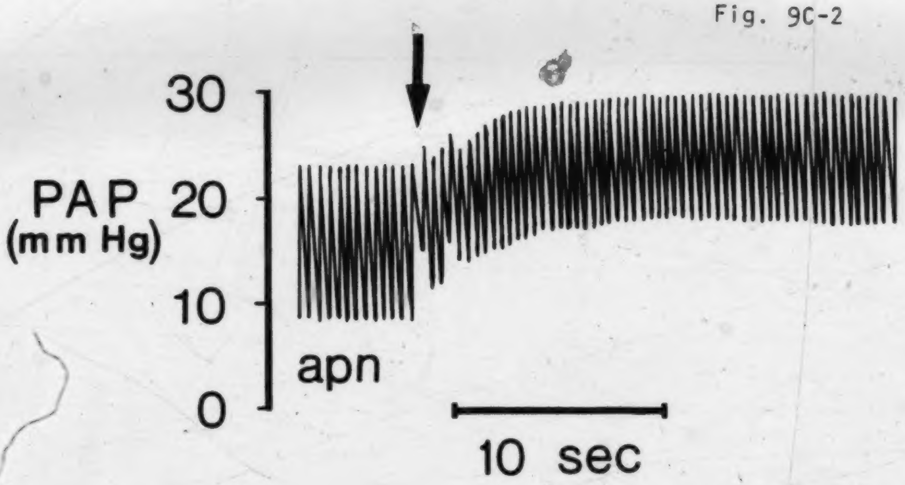

Figure 9C-1: Diagram of the circuit used for high-frequency ventilation, with the airway-pressure chamber connected to the endotracheal tube. HFOV, high-frequency oscillator, $\bar{P}aw$, airway pressure transducer, PEEP, underwater system to pressurize the airway-pressure chamber. Figure 9C-2: Effect of HFOV on the pulmonary artery pressure of a dog after a few seconds of apnea (apn). Arrow, start HFOV.

Chapter 9D: LUNG CLEARANCE OF RADIOACTIVE PARTICLES

INTRODUCTION

In the exeriments reported in Chapter 7 the effects of HFOV on mucociliary function were tested at the tracheal level. Although no differences with IPPV were observed, this does not discard the possibility that HFOV has a significant influence on the overall function of the mucociliary escalator. One way to test this possibility would be to assess the rate of clearance by the lung (LCR) of radioactively-marked inhaled particles.

In order to test the effects of HFOV on LCR, appropriate controls had to be obtained. Two approaches were considered: 1) one lung could be ventilated with HFOV (with a double-lumen ETT) and the other used as control (ventilated with IPPV); and 2) a given time period of IPPV could be used as control for HFOV measurements. To validate these approaches preliminary trials were designed to ascertain whether there was a correlation between LCR of regions of the right and left lungs and if LCR was constant over a given time period. Initially, a dual-probe scanner was used unsuccessfully; then the experiments were performed with a more sophisticated multiprobe scanner.

METHODS

Dual-probe experiments

A group of 10 mongrel dogs (weight range: 14--22 kg) were anesthetized with pentobarbital (30 mg/kg) and intubated with a 9 or

10 mm i.d. cuffed endotracheal tube. After a one-hour resting period (to allow for the acute effects of anesethesia to dissipate), the dogs were placed supine (on a specially designed table that secured the dog in a fixed position) and ventilated with a Harvard animal respirator (model 607) at a rate of 15 bpm and a V_T of 15 ml/kg. A T piece in the inspiratory line allowed connection of a nebulizer (DeVilbis #40) which contained a saline solution of sulfur colloid labelled with ^{99m}Tc. A manually-controlled valve allowed delivery of pressurized air (20 psi) into the nebulizer to generate the aerosol; nebulization was timed to coincide with the first half of the inspiratory time of the ventilator. Two collimator detectors (sodium iodide cystals; collimater apperture: 38 by 61 mm) were positioned over the mid-lateral region of each lung and connected to a dual-channel gamma analyzer (Picker Nuclear, dual probe model 2000). The dogs were ventilated with air containing radioactive aerosol for several breaths, until a sufficient amount of radiation was detected by the gamma analyzer (15,000--30,000 cpm). The nebulizer was then disconnected and the animals were either ventilated with the respirator (with the same settings) or allowed to breathe spontaneously. The count rates over the lateral lung regions were monitored for at least 2 h. Anesthesia was maintained at a light level with boluses of pentobarbital i.v.

Multiprobe experiments

These experiments were performed on a group of 6 dogs (weight range: 16--25 kg) anesthetized and intubated as described. The same protocol as for the dual probe experiments was followed for aerosol delivery. However in this case, count rates were monitored with a detector setup containing 8 collinear pairs of scintillation counters placed over the lungs of the supine dog. Count-rate data from each detector pair was collected via a "real-time" computer system and stored on magnetic disk for subsequent analysis.

Data analysis

The changes in count rates over time were fitted into an exponential equation by curvilinear regression analysis. The time necessary for a 50% drop in radiation counts in each region ($T^{1}/_{2}$) was obtained from the exponential equations, and corrected for the decay of the radioactive marker to obtain biological $T^{1}/_{2}$. A linear regression analysis was used to compare data obtained from corresponding regions of the right and left lungs over 1-h periods, or first versus second hour data from the same lung region.

RESULTS

Dual-probe experiments

The statistical analysis of the data showed that there was no significant correlation between LCR of the right and left lung regions during the first hour of scanning (Fig. 9D-1; r=0.29), or between the first and second hour within the right lung region (Fig.9D-2; r=0.46) or left lung region (Fig.9D-3; r=0.45). When the data were analyzed independently for animals ventilated with IPPV or breathing spontaneously, the correlations were also not significant.

Multiprobe experiments

No significant correlation was obtained between LCR of horizontally opposed right and left lung regions during the first hour of scanning; Fig.9D-4 shows a plot of data obtained from basal lung regions (r=0.32). There was no correlation between first and second hour LCR of the right (r=0.68) or left (r=0.23) lung regions. Fig.9D-5 shows the data obtained from the basal regions of the right lung during the first and second hours; Fig.9D-6 shows the same data for the corresponding regions of the left lung.

DISCUSSION

It is well known that the size of the particles (mass median aerodynamic diameter) is one of the most important factors that determines where a particle is deposited in the lung (1). About 50% of the 1-μm particles are deposited in the respiratory region (1); larger particles tend to be deposited preferentially in the airways. The size of ^{99m}Tc-sulfur colloid particles delivered by the nebulizer used in the present studies, was measured by a cascade impactor which gave the following results: activity mean aerodynamic diameter = 1.25 μm; geometric standard deviation = 1.80 μm. This implies that a significant fraction of the delivered aerosol was deposited in the respiratory region of the lungs, where it could not be cleared by the mucociliary function. The background radioactivity deposited in the respiratory zone could hamper detection of any drop in count rates in the airways (which represent a small fraction of the lung volume) due to the mucociliary function. The regions scanned during this study probably contained a significant number of intermediate-size airways which would tend to clear out aerosol but which would also receive a significant amount of aerosol from smaller airways. The balance of these two factors would determine the change in count rates over time detected externally (superimposed to the constant radioactivity coming from the respiratory zone which would remain quite stable during the period studied). All these factors combined may have contributed to the lack of correlation between $T^{1/2}$ measured in different lung regions (different influences of the factors) or during different time periods (not a single exponential function).

In a separate experiment in humans, the same type of aerosol was inhaled by 10 subjects and radioactivity over the whole lung monitored with a gamma camera. When the radioactivity measured was corrected for the decay of ^{99m}Tc, it was found that more than 95% of the aerosol was still present in the lungs 24 h after inhalations. From these results it could be speculated that: a) a significant number of particles were deposited in peripheral lung regions and could not be cleared by the mucociliary transport; b) the marker is bound tightly to the particles; c) no significiant amount of the marker is absorbed into the circulation.

In order to effectively assess mucociliary function, a much larger particle size would have to be used (probably larger than 10 or 15 μm). Also, the use of a gamma camera would permit a definition of regions of interest in the lung, which contain more airways. The decay of count rates in these regions would be a better reflection of mucociliary function.

As neither a generator of large particles nor an appropriate gamma camera were available, these studies were not done.

In summary, LCR of inhaled radioactive sulfur-colloid particles was monitored in dogs with either dual or multiprobe radiation detectors during SB and IPPV. No correlation could be found between LCR of coresponding regions of the right and left lungs or between first- and second-hour LCR of individual lung regions. This lack of correlation was probably due to both the small size of the radioactive particles and to the low spatial resolution of the scanning systems used.

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Fig. 9D-1

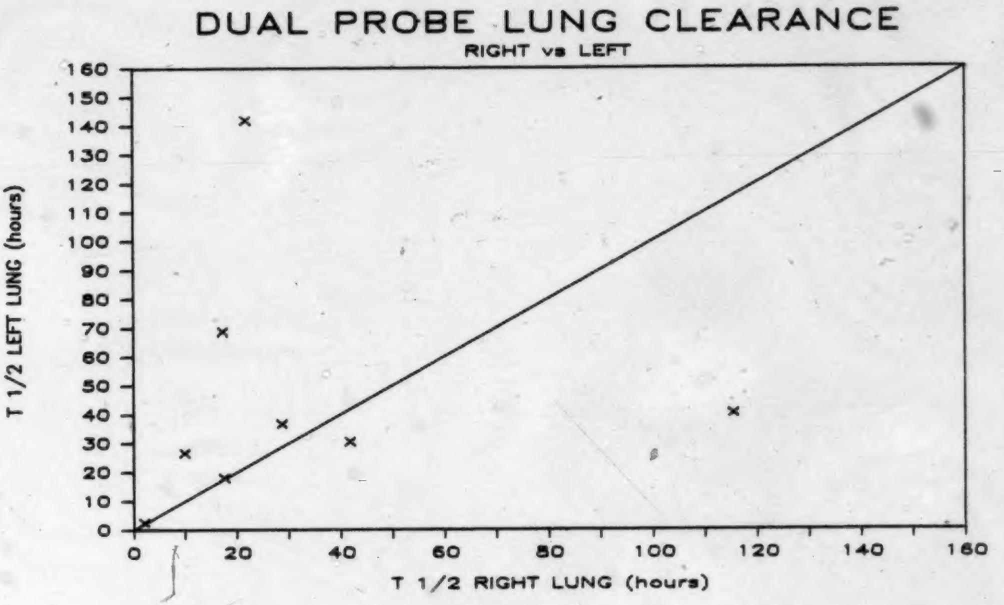
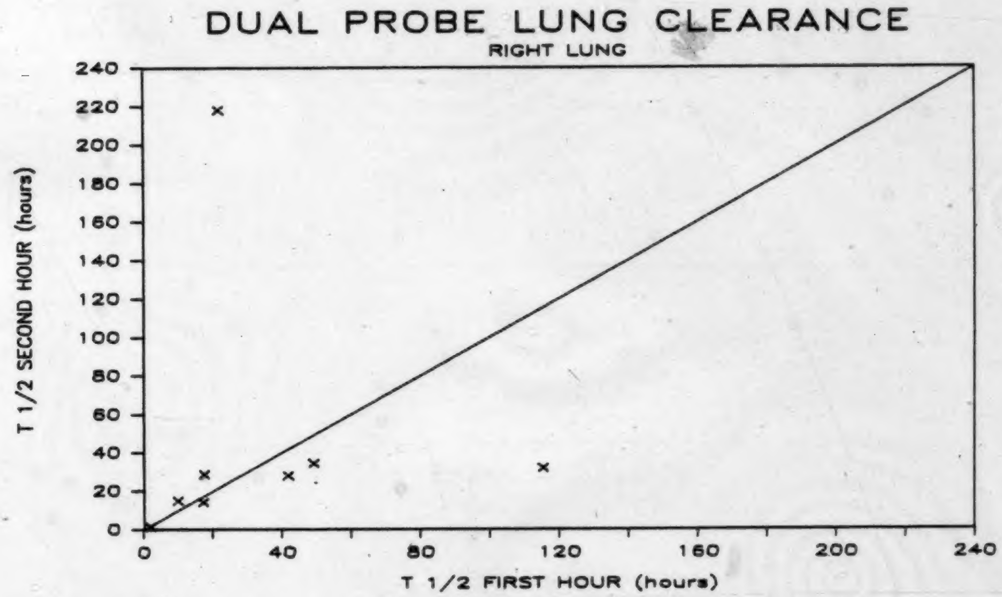


Fig. 9D-2



Figures 9D-1 and 9D-2: Clearance rates (T½) measured with a dual probe, of right and left lung (top); and right lung comparing 1st versus 2nd hour (bottom).

Fig. 9D-3

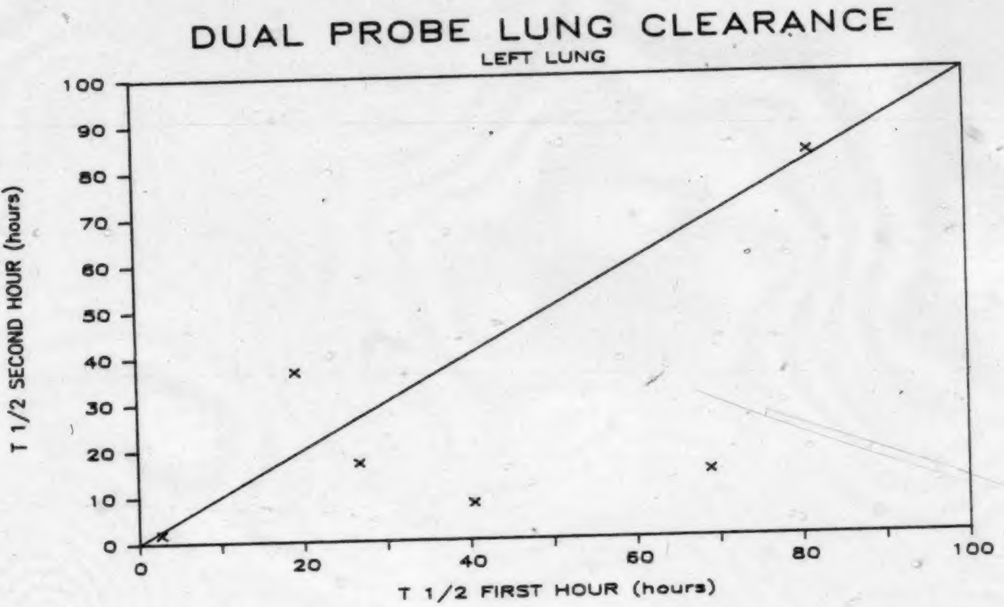
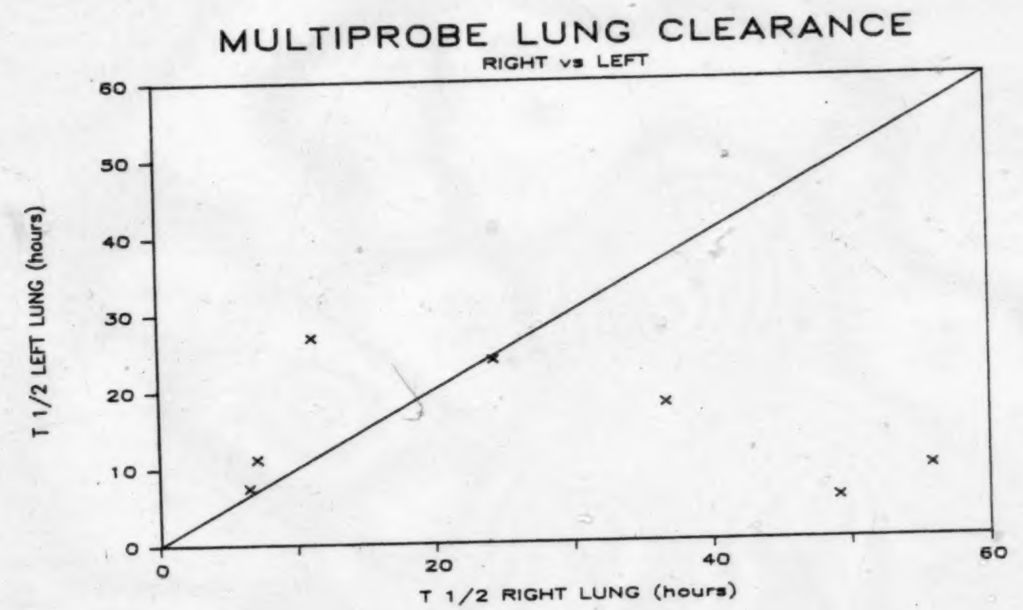
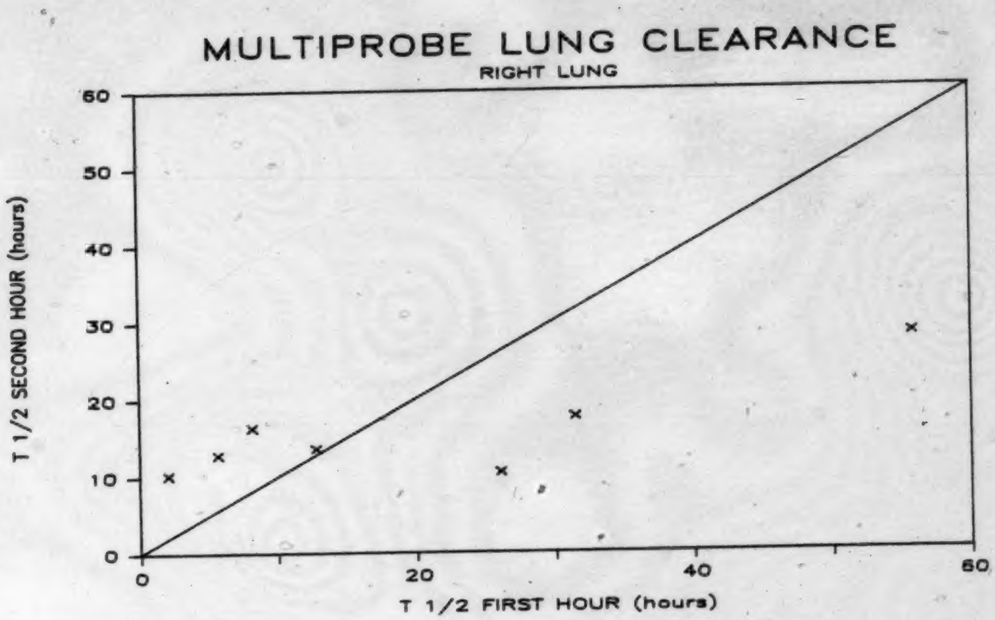


Fig. 9D-4



Figures 9D-3 and 9D-4: Clearance rates ($T_{1/2}$) measured with a dual probe on the left lung, comparing 1st versus 2nd hour (top); and measured with a multiprobe, comparing right versus left lung (bottom).

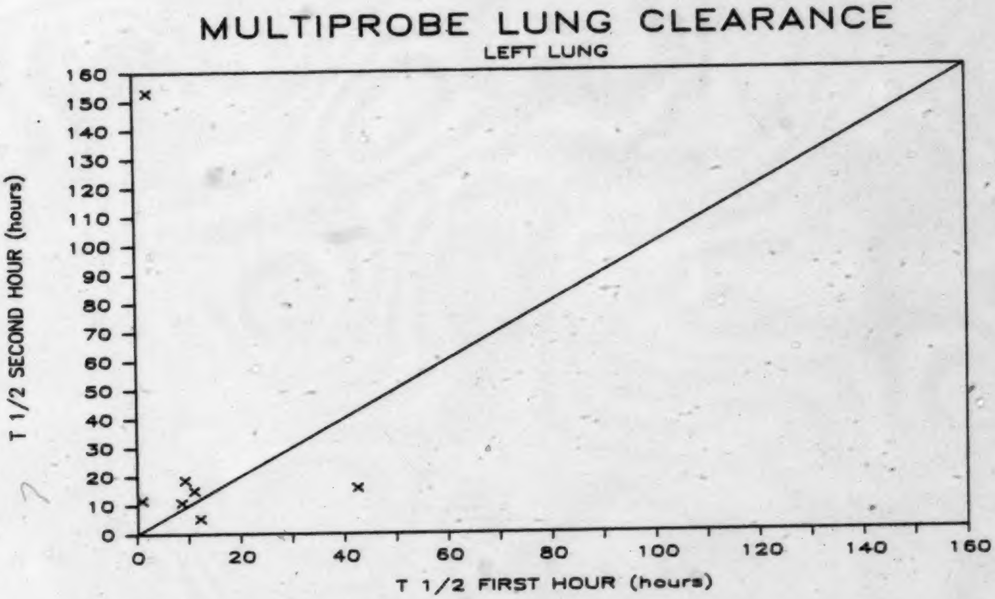
Fig. 9D-5



MULTIPROBE LUNG CLEARANCE

RIGHT LUNG

Fig. 9D-6



MULTIPROBE LUNG CLEARANCE

LEFT LUNG

Figures 9D-5 and 9D-6: Clearance rates (T½) measured with a multiprobe on the right (top) and left (bottom) lungs, comparing 1st versus 2nd hour.

Chapter 9E: USE OF A FIXED-VOLUME PUMP TO VENTILATE SMALL ANIMALS

INTRODUCTION

In Appendix I it is stated that the HFOV pump used for this thesis delivered a fixed volume, and the size of the animals had to be accomodated to it; the optimal size of animals that could be ventilated with this pump was around 6--8 kg. Due to the possible application of HFOV to pediatric use, the following tests were done to develop a method to deliver a small V_T with the same pump. By trial and error, a modification of the circuit was developed, which induced satisfactory gas exchange in small cats.

METHODS

Two cats (2.0 and 2.8 kg) were anesthetized with pentobarbital and intubated with a 4 mm i.d. cuffed ETT. An animal ventilator (Harvard model 607) was used for IPPV (rate, 25 bpm; V_T 15 ml/kg). The standard HFOV circuit was modified to reduce the V_T reaching the lungs. This modification consisted of a T piece that was placed on the inspiratory catheter of the circuit, and connected to 60 cm of large-bore (9 mm i.d.) Tygon tubing (this circuit was similar to Fig.AI-6D); the distal end of this tubing was immersed under 5 cm of H_2O to maintain an adequate $\overline{P}aw$. The sizes of the components of this circuit were determined on a trial-and-error basis. The frequency of the pump was varied between 10 and 30 Hz, and bias flow between 0.1 and 5 L/min. Samples for blood gas analysis (Instrumentation Laboratory model 113) were taken after at least 10 min of IPPV or HFOV at a fixed setting.

RESULTS

Figure.9E-1 shows values of PaO_2 obtained during HFOV in the two cats (calculated as % of IPPV measurements) and $PaCO_2$ data. PaO_2 was usually similar to IPPV levels (± 20%) and showed a tendency to decrase with increased frequency. $PaCO_2$ could be maintained at very low levels, and did not fluctuate much with variations in HFOV rate or bias flow.

DISCUSSION

The results of this study indicate that a fixed-volume HFOV pump can be used effectively to ventilate small animals by inducing a controlled leak in the inspiratory line. The low $PaCO_2$ levels obtained in normal animals suggests that the system could be effective in the ventilation of animals with abnormal lungs. The leakage circuit used in the present studies acts as an inefficient low-pass filter which leaks part of the V_T. A certain "PEEP" level was necessary to maintain the lungs distended. Other designs that induced a smaller leak, had the tendency to cause hypotension; a larger leak was associated with an increase in $PaCO_2$ and decrease in PaO_2. It is likely that a similar system could be used to ventilate even smaller animals by increasing the proportion of V_T leaked, but it would have to be adjusted in each case depending on the size of the lungs and their mechanical characteristics (especially Cst and Raw). The small effect of the change in rate and bias flow on $PaCO_2$ suggests that the alveolar ventilation induced, was sufficient to achieve an optimal gas exchange.

Fig. 9E-1

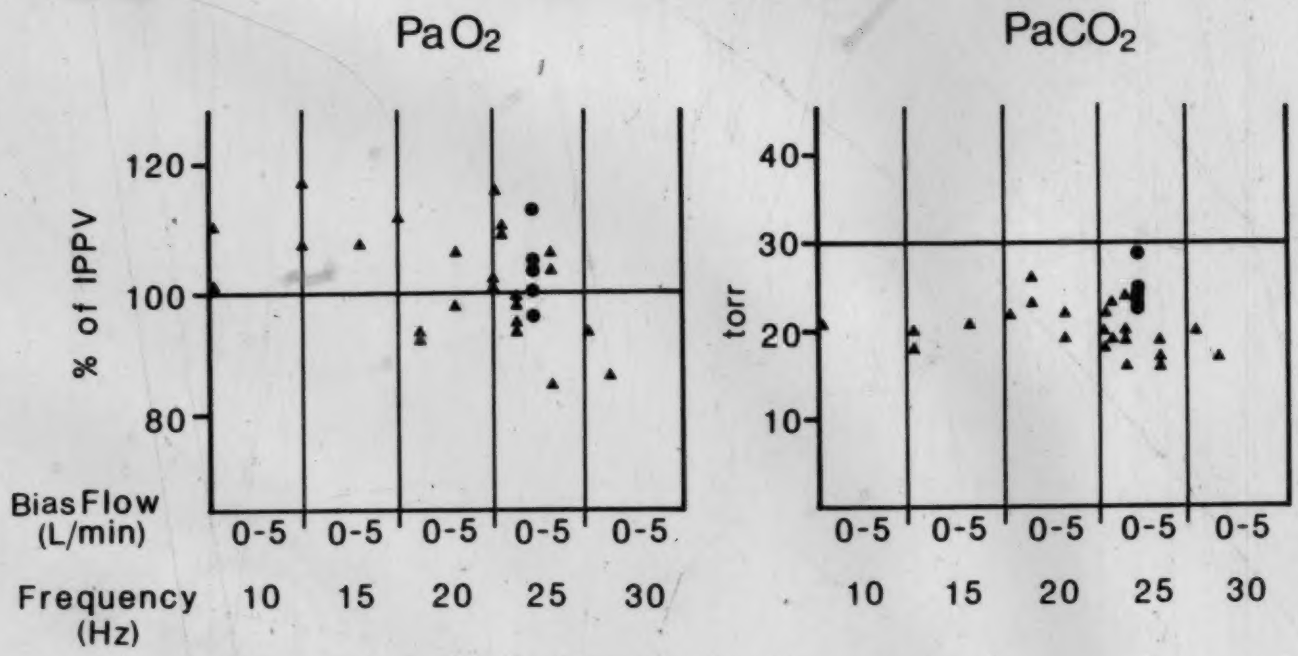


Figure 9E-1: Arterial PO_2 and PCO_2 of two cats at different frequencies and bias flows.

Chapter 9F: PRELIMINARY STUDIES VITH HFOV IN DOGS WITH OLEIC ACID INDUCED LUNG INJURY

INTRODUCTION

In order to prove the usefulness of HFOV in a clinical setting, its performance in the ventilation of diseased lungs had to be tested. Initially, a complete study with an OA lung injury model was planned, but when the important effects of HFOV on cardiovascular function of normal animals were observed, the OA studies were not continued and efforts were directed towards the understanding of the mechanisms behind the observed impairment of cardiovascular function in dogs with normal lungs. Moreover the OA injury has complex physiological effects on the body, including changes in lung permeability and pulmonary and systemic circulation. A more convenient lung injury model is probably the saline lavage described in Appendix IV, which has a more selective effect on lung mechanic parameters and less hemodynamic repercussion.

The following is the description of the preliminary trials with an OA lung injury model

METHODS

After the experiments described in Chapter 1 had been completed in three of the dogs, pulmonary edema was induced in them by injecting a bolus of 0.075 ml/kg of oleic acid into the right ventricle. After 2 hours of IPPV, these animals were ventilated with HFOV alone (25 Hz, bias flow 4 L/min) or HFOV (25 Hz, no bias flow) superimposed on IPPV. To achieve the latter, a 62.5-ml plastic chamber (airway pressure chamber) enclosed the HFOV catheters and the proximal endotracheal tube (Fig.4-1). One side of the chamber was connected to the inspiratory port of the Harvard ventilator and the other side to the expiratory port. During HFOV alone, the chamber was continuously flushed with 15 L/min of air to avoid CO_2 retention. In these studies, hemodynamic data and blood samples for gas analysis were taken 10 minutes after each ventilatory setting was started and at the end of the 2-hour IPPV period.

RESULTS

The results of the HFOV studies in dogs with pulmonary edema are presented in Fig. 9C-1. The injection of oleic acid induced a substantial decrease in PaO_2 during IPPV, $PaCO_2$ changed little and $\overline{SAP}$ decreased slightly. HFOV maintained PaO_2, $PaCO_2$ and $\overline{SAP}$ levels similar to the IPPV values. However, when HFOV was superimposed on IPPV, PaO_2 increased, $PaCO_2$ decreased, and $\overline{SAP}$ decreased slightly.

DISCUSION

The preliminary results obtained after oleic acid injection support previous data suggesting that HFOV is similar to IPPV in gas exchange during pulmonary edema and is capable of supporting ventilation and oxygenation (see Introduction). The fact that gas exchange was better when HFOV was superimposed on to IPPV may be due to the effect of a distending pressure that opened airways that were partially filled with fluid. Indeed, in all the animals abundant frothy hemorrhagic secretions appeared in the proximal end of the ETT. It can be speculated that these secretions represent a physical barrier to the movement of gases in small airways when a small V_T is used, like during HFOV. The large V_T used during IPPV could probably overcome this barrier, at least partially, allowing the superimposed oscillation to reach some respiratory units.

Fig. 9F-1

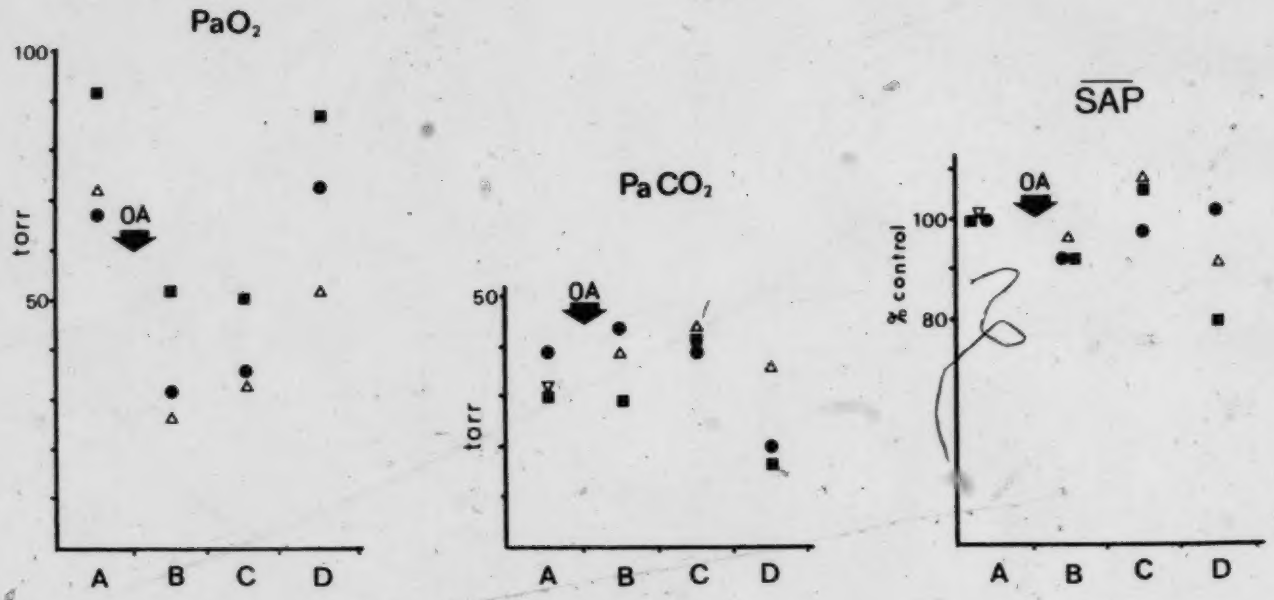


Figure 9F-1: Arterial PO$_2$ and PCO$_2$, and mean systemic arterial pressure of three dogs with oleic acid lung injury during IPPB (B), HFOV (C) and HFOV superimposed to IPPV (D). A, control values previous to injury

APPENDIX

APPENDIX I

DESCRIPTION AND CHARACTERIZATION OF THE HFOV SYSTEM

DESCRIPTION OF THE PUMP

The pump consists of a 70-mm diameter standless-steel metal bellows, welded to two steel plates (Fig.AI-1). The bottom plate is attached to an eccentric cam through a connecting rod, and driven by a variable-speed DC motor (frequency 1—32 Hz); a sealed ball bearing in the cam helps minimize friction and a counterweight decreases vibration. The top plate has two openings that correspond with two apertures in the pump casing (to which the plate is bolted). Between the upper plate and the casing there is a teflon disk with two orifices that contain thin steel plates that act as unidirectional valves, one for intake and the other for exhaust of gases from the bellows chamber. Two short brass tubes (20 mm length, 5 mm i.d.) screwed into the casing apertures allow connection of the plastic tubings of the HFOV circuit. This type of pump is used in the industry for tasks such as sampling hot gases from furnaces and smoke stacks or pumping fuel in aircraft, and is very rugged and reliable. According to the manufacturer (Metal Bellows Corporation, Sharon, MA), the pump is extremely airtight (leakage less than 10^{-4} ml He/sec) and designed to work at frequencies of up to 50 Hz uninterrupted for more than a year.

In preliminary trials it was found that the pump tended to heat up at high frequencies. To avoid heating, an aluminum plate with multiple holes was secured in front of the pump and a high pressure jet of air with nebulized distilled water was directed onto it; another jet sprayed water directly onto the pump bellows. A thermistor secured to the inside wall of the exhaust tubing was used to monitor gas temperature during the experiments. This cooling system was very effective (Fig.AI-2), and inspired gas temperature could be adjusted to as low as 26°C;

but to prevent hypothermia temperature was kept around 36ºC.

The stroke volume of the pump was measured by water displacement and found to be 25.5 ml; the bellows dead space volume (to the valve level) was 5.5 ml.

VALVE PERFORMANCE

According to the manufacturer, the valves are functional even at high frequencies and able to sustain a vacuum or compression pressure of hundreds of torr. To check the functionality of the valves several tests were performed. Unfortunately, the bellows chamber could not be drilled to obtain internal pressure readings which would have been helpful in the performance testing.

For the first test the exhaust port was connected to a long tube (length 8 m, 6 mm i.d.) which had a high pressure gauge at the end. The tube dampened the pressure oscillations and allowed direct readings from the gauge. The system was tested over a wide range of frequencies; the results are shown in Fig.AI-3. At frequencies of 15 Hz and higher the system reached pressures above 2000 mm Hg; at lower frequencies the motor stalled. These results suggest that the outlet valve was functional at high frequencies and could generate pressures well above those expected during the animal experiments. In a second test, a short plastic tube was attached to the pump outlet; the distal end of the tube was covered with a fine wire screen (400 mesh). A pressure transducer (Validyne MP45) was connected to the wall of the plastic tube. This system acted as a flowmeter, and although it was not calibrated, it was used qualitatively to monitor flow direction. With the pump running at full speed (32 Hz), no negative flow could be detected when the positive flow created a full scale signal on an oscilloscope. This meant that the back flow (volume suctioned if the valve had been failing) was less than 1% of the stroke volume. When a vacuum was created by partially occluding the pump inlet, no negative flow signal could be detected. A similar test was performed by attaching the flowmeter to the pump inlet, and no valve failure could be detected.

When V_T, delivered by the pump over a wide range of frequencies, was measured using a low compression system (see later), no drop in volume was observed (Fig.AI-4) as frequency increased and the average value (25.43 ± 0.67) was close to the stroke volume obtained by water displacement, indicating a satisfactory valve performance.

DEVELOPMENT OF THE RESPIRATORY CIRCUIT

Initial Model and Subsequent Modifications: The first trial on the HFOV pump was attempted with a circuit designed to match, as closely as possible, standard HFOV systems (Dr. A.C. Bryan, personal communication, and Ref.1, Chapter 9C) A diagram of the circuit employed is shown in Fig. AI-5A. The first animals used were two mongrel dogs with a weight of 17.5 kg and 17.8 kg, respectively. The animals consistently showed a decrease in PaO_2 and an increase on $PaCO_2$ within a few minutes of being switched from IPPV (15 ml/kg at 15 bpm) to HFOV. There were no immediate $\overline{SAP}$ changes. These two animals showed very poor oxygenation and CO_2 removal at frequencies ranging from 10 to 30 Hz and side flows of fresh air of 1 to 16 L/min. The sizes and lengths of the tubes used as a low pass filter (LPF, Fig.AI-5A) were modified over a wide range without substantial improvement in the blood gases. In the second dog, an attempt was made of using only the outlet of the pump, trying to mimic systems that work as HFPPV (Fig.AI-5B); however, the arterial blood gases did not improve. Subsequently a different system was tested, trying to modify the aerodynamics of the "inspiratory" circuit (Fig.AI-5C). With this modification, the $PaCO_2$ decreased from the previous values of 55--65 torr to less than 50 torr at frequencies ranging between 20 and 30 Hz and side flows of 5 to 15 L/min of air.

Dog #3 (16.1 kg) was tried with the circuit shown in Fig.AI-5C but with higher side flows of air (20 to 33 L/min). The blood gas values improved, with a decrease in $PaCO_2$ to the low forties; the PaO_2 also showed an improvement rising from values below 50 torr to 60—75 torr. The best results were obtained with 30 Hz, a LPF 750 mm (9mm i.d.), 33 L/min of fresh air flow and 3 cm of PEEP LPF immersed 3 cm underwater): PaO_2 rose to 80 torr and $PaCO_2$ fell to 45 torr after 15 min of HFOV. But $\overline{P}$pl (measured with a pleural catheter and water manometer) rose from -5 (apnea) to +7 cm H_2O and there was also a substantial drop in $\overline{SAP}$.

Intermediate Steps: It was postulated that a major problem with the system studied could be that the V_T delivered by the pump was too small for the size of the dogs. As the fixed stroke volume was an unmodifiable characteristic of the pump, it was decided to use smaller animals.

The next experiments were done with dogs ranging from 6 to 9 kg. The first trials with the circuit depicted in Fig.AI-5C showed better ventilation and oxygenation, but $PaCO_2$ was always above 40 torr.

The next step was then to develop another circuit with the hope it would work better. Many systems and a wide range of designs were tested without success; the diagrams of some of the circuits used are shown in Fig.AI-6. The parameters monitored were: PaO_2 and $PaCO_2$ to assess gas exchange, $\overline{\text{Ppl}}$ as an index of changes in FRC, and $\overline{\text{SAP}}$ as a measure of cardiovascular performance. The different circuits were tested on a trial and error basis, trying to cover a wide range of designs. The unidirectional valves were removed but CO_2 removal worsened. Finally, after an over-simplification of the system, a setup was obtained with good performance; this system is described as the "2-W" circuit.

Description of the 2-W circuit: This circuit is depicted diagramatically in Fig.AI-7. It consists of two short (30 mm) semi-rigid thin-walled plastic catheters (3 mm i.d.), connected to the inlet and outlet of the HFOV pump with short pieces (30 mm) of flexible plastic tubing (9 mm i.d.). The tips of the two catheters were glued 15 mm into a rigid plastic connector (9 mm o.d.) attached to the proximal end of the ETT. The 3-mm catheters were the widest that would fit into the ETT connector without distortion (narrower catheters were less effective). A 14 G needle was introduced through the wall of the inlet flexible plastic tubing, 5 mm into the lumen, and pointed towards the inlet valve; it was used to add fresh air to the circuit (bias flow). The flows of air were measured with a calibrated glass rotameter (Cole-Parmer #4 Chicago, IL). All the connections had an air-tight seal, except where the two catheters entered the ETT connector where a fixed leak was maintained throughout the experiments. For some studies, a large chamber (airway pressure chamber) was fitted around the proximal end of the ETT to ensure proper air conditioning or to change $\overline{\text{Paw}}$; it will be described in the corresponding chapters.

The range of frequencies tested was 15 to 30 Hz. Lower frequencies were avoided because of poor results on preliminary trials. Bias flows of air of 1 and 4 L/min were found to be appropriate for the size of animals studied. With this circuit $PaCO_2$ was usually below 35 torr, and in some cases as low as 25 torr; PaO_2 was usually above 70 torr in dogs with normal lungs (see Chapter 1).

TIDAL VOUME MEASUREMENTS

Two methods were used to measure the V_T delivered by the pump: a bell spirometer and a plethysmograph. The spirometer was used to measure the pump stroke delivered at the pump outlet, through a low-resistance system. The plethysmograph measured V_T coming out of the ventilator catheters, which could be expected to create a high resistance load for the pump.

Spirometric measurements:The pump's outlet was connected to a 9 L bell spirometer (Collins model 6001) through a 25-cm large-bore tubing (12.7 mm i.d.). A 20 G needle directly attached to a miniature transducer (Statham model P50) was inserted through the tubing wall; the amplified output of the transducer was displayed on a strip-chart recorder (Hewlett Packard model 7784A) and used to calculate pump frequency and testing time (Tt). The pump frequency was set at random from 5 to 32 Hz. Tidal volume was obtained from the volume delivered to the spirometer (Vs) during the test period, (Tt), and the pump frequency (f); the formula used was:

$$V_T = Vs/(Tt \times f)$$

The results of the test are presented in Fig.AI-4; calculated V_T was quite stable over the range of frequencies tested, and averaged 25.43 ± 0.67 ml, which is in close agreement with the 25.5 ml obtained by water displacement.

Plethysmographic measurements: A plethysmograph was constructed out of a 19 L airtight Plexiglas box (wall thickness: 12.7 mm) filled with steel wool (to minimize adibatic effects on chamber pressure). Box pressure (Pbox) was measured with a MP45 Validyne transducer which was connected to the box with 4 cm of plastic tubing (3 mm i.d.). The catheter-transducer system had a flat frequency response up to at least 50 Hz (tested by the Jackson and Winegar's method); the resonant frequency of the box-transducer system was 117 Hz, obtained by the transient method (Milnor, W.R. Hemodynamics. Baltimore: Williams and Wilkins, 1982, pp. 289-291) A narrow tubing with very high impedance was used to connect the box interior to the negative port of the MP45 transducer, to reduce the drift in pressure readings induced by Pbox fluctuations due to HFOV, and allow the use of high gain in Pbox readings. The tubing was effective in dampening Pbox oscillations down to less than 2% at frequencies above 2 Hz, and thus induced minimal error in the V_T measurements obtained from Pbox oscillations. An 8 cm piece of ETT (9 mm i.d.) was used to connect the HFOV circuit to a port (8 mm i.d.) in the box wall. To calibrate the plethysmograph, known volumes of air were injected into the box and Pbox recorded; the system was linear (± 3%) up to at least 50 ml, which induced a Pbox of 2.6 cm H_2O.

For the first test, the HFOV circuit described previously was used but without the bias-flow needle and with the space between the ETT and the 3-mm catheters filled with plastic putty to obtain a closed system and avoid air leaks or entrainment. Fig.4 shows the V_T values calculated from Pbox oscillations between 5 and 32 Hz. Up to 14 Hz, V_T changed little and agreed with spirometric measurements; above this frequency V_T decreased to around 22 ml at 20 Hz and 17 ml at 32 Hz.

Next, V_T was measured without occluding the ETT connector, but with the ETT tip and pump catheters enclosed in a 290-ml Plexiglas chamber (airway pressure chamber, Chapter 4). V_T was some 3 ml lower than before at frequencies below 14 Hz (Fig.AI-4); above 14 Hz the difference decreased slightly as pump frequency increased. When V_T was measured without the airway pressure chamber, similar results were obtained (Fig.AI-4). These results suggest that there was no air entrainment around the pump catheters because V_T at low frequencies was comparable to the spirometric values, and decreased at high frequencies; also when an open system was used, V_T was lower than with a closed system. The lower V_T seen with the open system was probably due to leakage around the pump catheters, which was influenced very little by the airway pressure chamber.

The lower V_T at high frequencies (compared to spirometric values) was probably due to the higher resistance of the pump catheters, which likely induced significant volume compression.

In another set of tests, the effect of catheter diameter on V_T was investigated. Four different catheters were used with an unoccluded circuit: 3 mm, 2.8 mm, 2.5 mm and 1.6 mm i.d., all of similar lengths; the results are presented in Fig.AI-7b. The 2.8 mm catheter induced higher V_T than the 3 mm catheter, and at intermediate frequencies V_T was slightly higher than the spirometric values (compare with Fig.AI-8). This was probably due to air entrainment induced by the higher air velocities at the catheter tip, that "compensated" (and in some cases over-compensated) for the leakage volume; at high frequencies the higher resistance of the catheters was probably responsible for the decrease in V_T. The same trend, but more accentuated, was observed with the 2.5-mm catheters which probably induced higher V_T by entrainment at low frequencies and a larger compression-induced drop in V_T at high frequencies. The 1.6-mm catheters at 7 Hz induced the highest V_T of all the systems, but at higher frequencies V_T fell rapidly reaching values below 10 ml at frequencies above 20 Hz, probably due to the very high resistance of the narrow catheters causing compression.

In the last group of tests, the effect on V_T of changing chamber pressure was investigated. The 3-mm catheters were used unoccluded, with the airway chamber pressure in place. The chamber was connected to both a compressed air and a vacuum source that could be adjusted to induce different chamber pressures. The pump was set at 20 Hz, with no bias flow; V_T was measured with the plethysmograph at chamber pressures between -20 and +24 cm H_2O. Fig.AI-9 shows V_T plotted against chamber pressure; V_T varied only slightly when chamber pressure changed, the average value being 20.61 ± 0.42 ml. These results indicate that the pressure in the airway chamber had only a minor effect on V_T.

LUNG MODEL MEASUREMENTS

A lung model was constructed using a latex balloon with several thin sheets of latex wrapped around it to induce a compliance similar to dog lung values. The compliance ranged from 52.9 ml/cm H_2O at a balloon volume of 550 ml, to 19.2 ml/cm H_2O at a volume of 750 ml. One end of the balloon was attached to a 9 mm i.d. ETT and in the other a miniature blood-pressure transducer (Statham model P50) was introduced without the plastic dome attached (to optimize its frequency resonse, which according to the manufacturer is flat up to at least 200 Hz) to measure balloon pressure (Palv). The HFOV circuit was connected with the 3-mm catheters unoccluded and the airway pressure chamber in place.

The first test was performed with a bias flow of 4 L/min and varying pump frequency. As frequency increased, $\bar{P}$alv increased linearly (linear correlation coefficient, $r = 0.90$; $p<0.001$); pulse pressure increased up to 20 Hz and then remained stable (Fig.AI-10). This increase in $\bar{P}$alv with frequency can be explained, at least in part, by a Bernoulli phenomenon: kinetic energy of the air molecules rose with frequency, and was transformed into potential energy (measured as $\bar{P}$alv) when velocity decreased inside the balloon. The balloon's neck was semi-rigid, thus the increase in $\bar{P}$alv cannot be explained by air trapping due to "airway" collapse. The same test was repeated but maintaining $\bar{P}$alv constant around 10 cm H_2O (by adjusting airway chamber pressure) and no bias flow. In this case Palv pulse was quite constant, and only decreased slightly at frequencies above 20 Hz (Fig.AI-11). These results indicate that increasing HFOV frequency tends to raise $\bar{P}$alv (and volume of the model) linearly. Pulse pressure decreases slightly at high frequencies - may be due to a decrease in V_T, as mentioned above - unless model volume is allowed to rise to less compliant parts of the P/V curve. The lack of increase in pulse pressure at high frequencies, when $\bar{P}$alv was maintained stable, rules out significant air entrainment. The resonant frequency of the system was not tested.

In another test, frequency was maintained at 20 Hz and bias flow was varied from 0 to 30 L/min; $\bar{P}$alv and pulse pressure rose as bias flow increased (Fig.AI-12). When $\bar{P}$alv was measured at different bias flows, with the pump stopped, a rise in $\bar{P}$alv was obtained that ran almost parallel to the HFOV values (Fig.AI-12). This suggests that, during

HFOV, increasing bias flow raises $\bar{P}alv$ mostly due to the back pressure created inside the lung by the air flow. The back pressure induced by flows below 10 L/min was very small; also, as the system is open, $\bar{P}alv$ can be decreased to any desired level, by lowering the pressure in the airway chamber.

CONCLUSION

In summary, this HFOV system uses a stainless steel bellows with high frequency unidirectional valves, connected to the airway by two 3 mm i.d. catheters introduced into the proximal ETT; the valves are functional up to at least 32 Hz. The bellows delivers a V_T of approximately 25.5 ml, but part of it is lost, probably due to compression at high frequencies and leaks at the proximal tip of the ETT. V_T delivered into the lungs at 20 Hz is around 22 ml. No significant air entrainment takes place unless narrower catheters are used. A chamber enclosing the catheters and tip of the ETT permits adjustment of $\bar{P}alv$; varying this chamber pressure does not affect delivered V_T. Tests using a lung model suggest that increasing frequencies raise $\bar{P}alv$, as does bias flow. The frequency-dependent raise in $\bar{P}alv$ is probably related to a Bernoulli phenomenon; the bias-flow-related increase can be explained by the back pressure created in the system by the flow of air.

Fig. AI-1

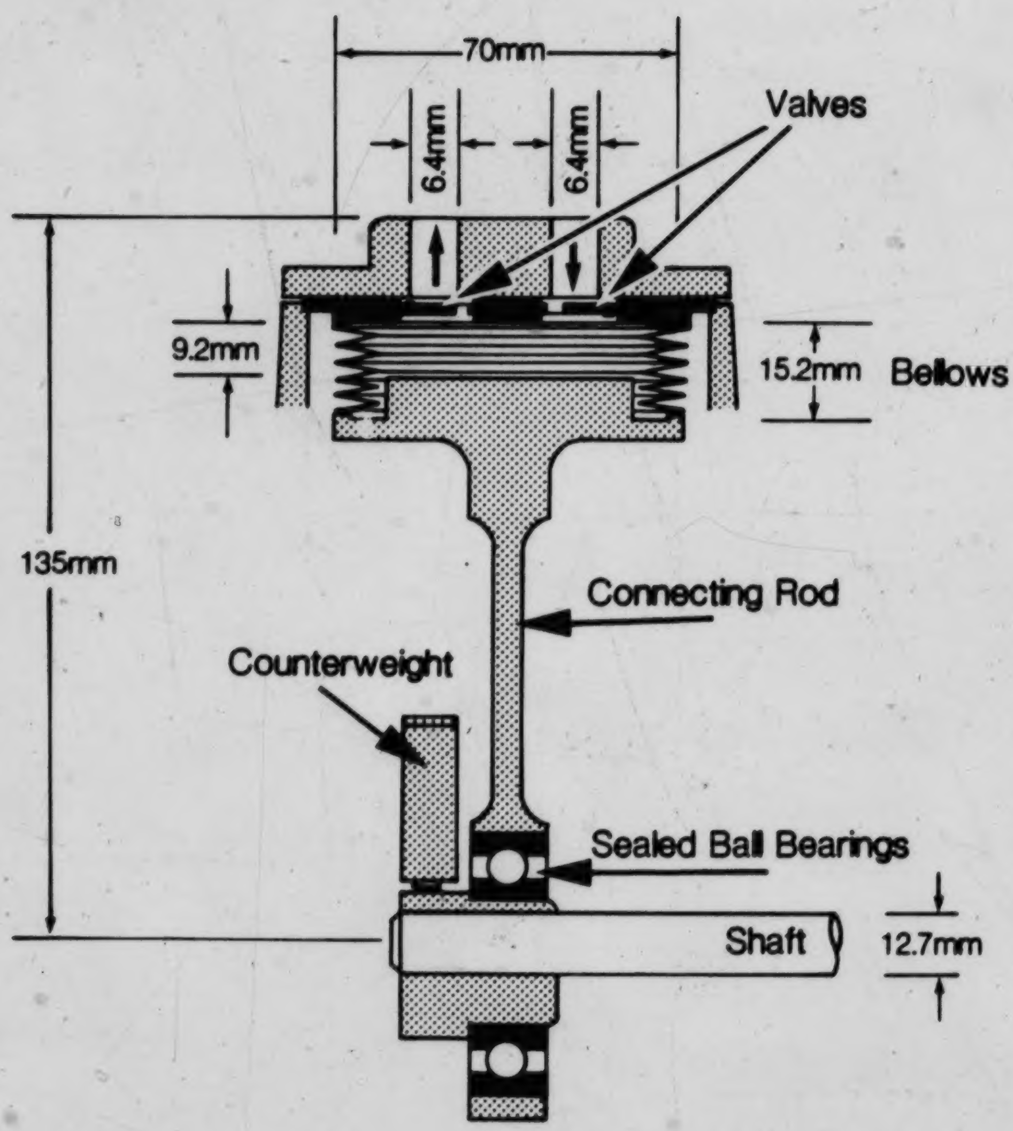

70mm
Valves
6.4mm
6.4mm
9.2mm
15.2mm
Bellows
135mm
Connecting Rod
Counterweight
Sealed Ball Bearings
Shaft
12.7mm

Figure AI-1: Diagram of the bellows pump. For details, see text.

Fig. AI-2

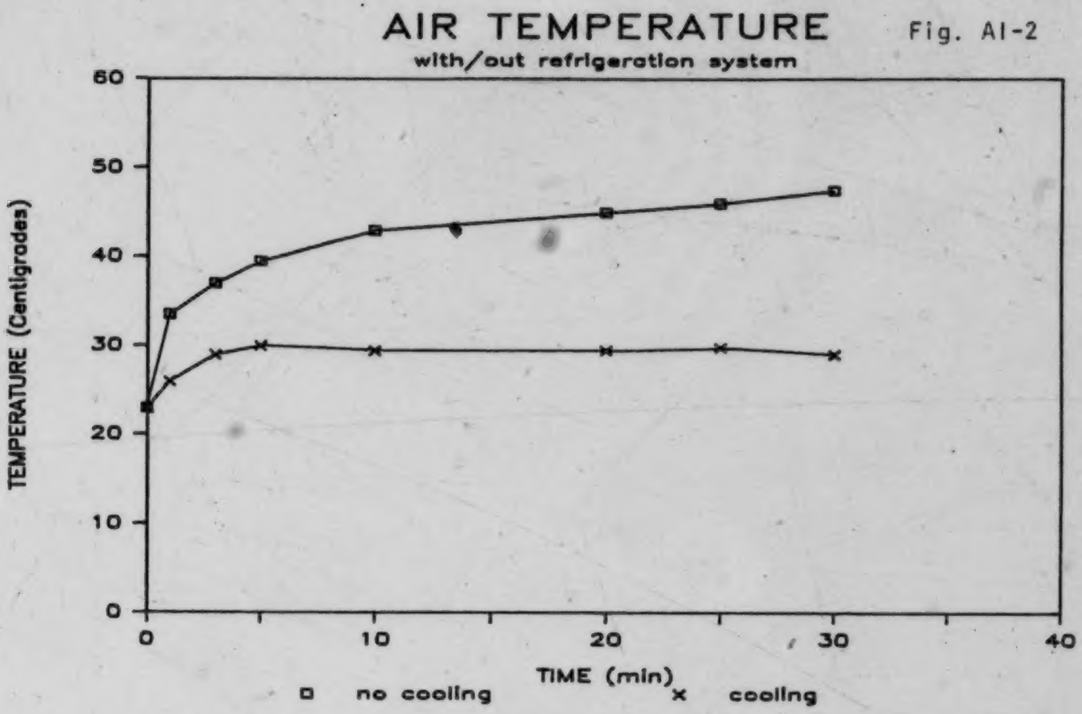


Fig. AI-3

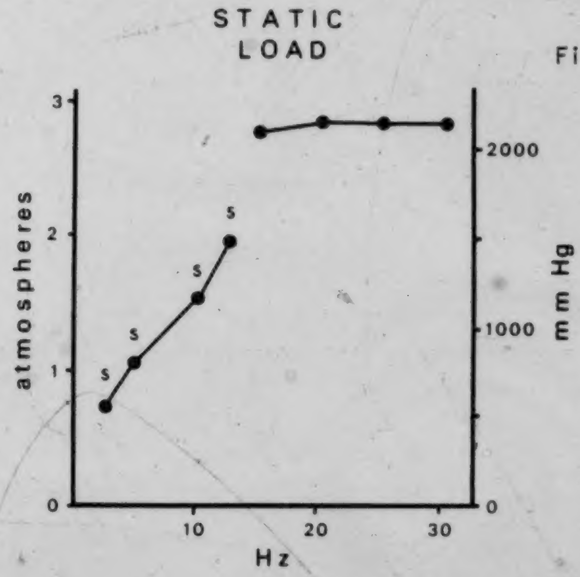


Figure AI-2: Change in outlet air temperature over time, during HFOV, without (squares) and with (crosses) a cooling system. Figure AI-3: pressure delivered by the HFOV pump in a closed circuit at different frequencies

Fig. AI-4

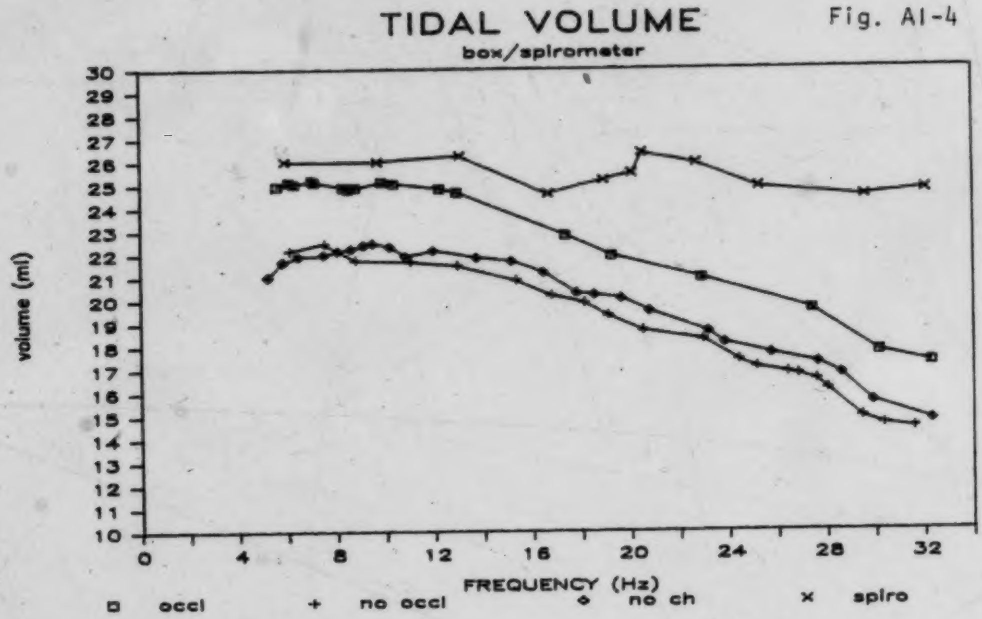


Fig. AI-5

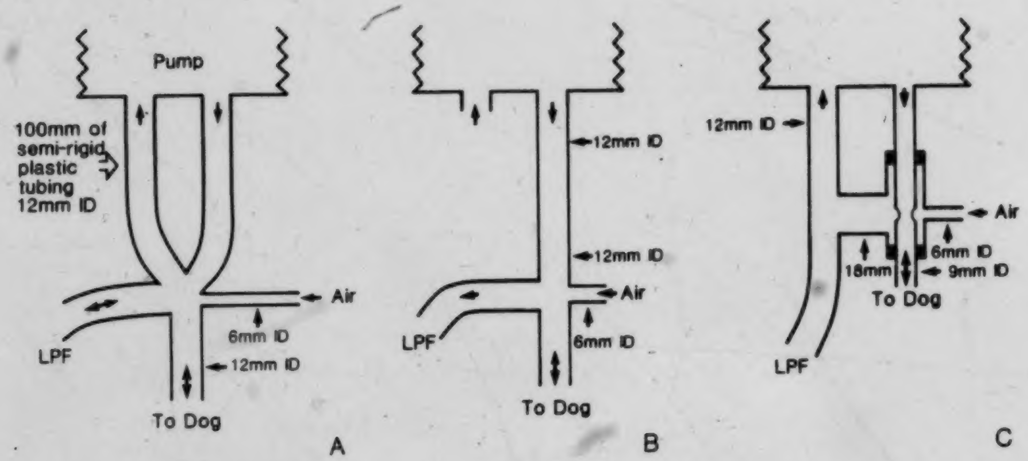

Pump
100mm of semi-rigid plastic tubing 12mm ID
Air
LPF
6mm ID
12mm ID
To Dog
A
12mm ID
12mm ID
Air
LPF
6mm ID
To Dog
B
12mm ID
Air
6mm ID
18mm
9mm ID
To Dog
LPF
C

Figure AI-4: Tidal volume delivered by the HFOV pump with an occluded system, open airway pressure chamber, without chamber and directly into the spirometer. Figure AI-5: Three HFOV circuits tried initially.

Fig. AI-6

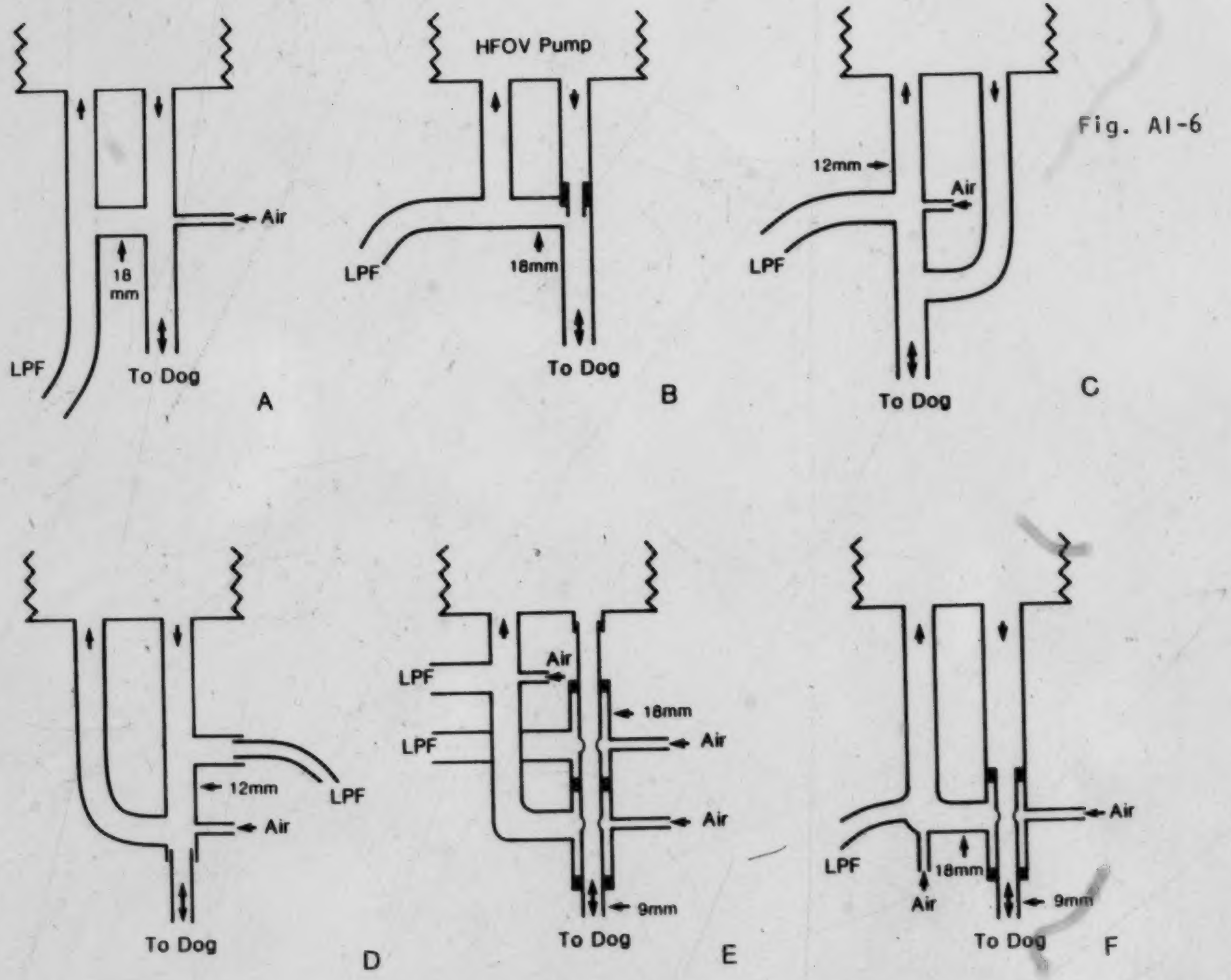

HFOV Pump
Air
18 mm
18mm
12mm
9mm
LPF
To Dog
A
B
C
D
E
F

Figure AI-6: Six of the HFOV circuits tested in a late phase. For details see text.

Fig. AI-7

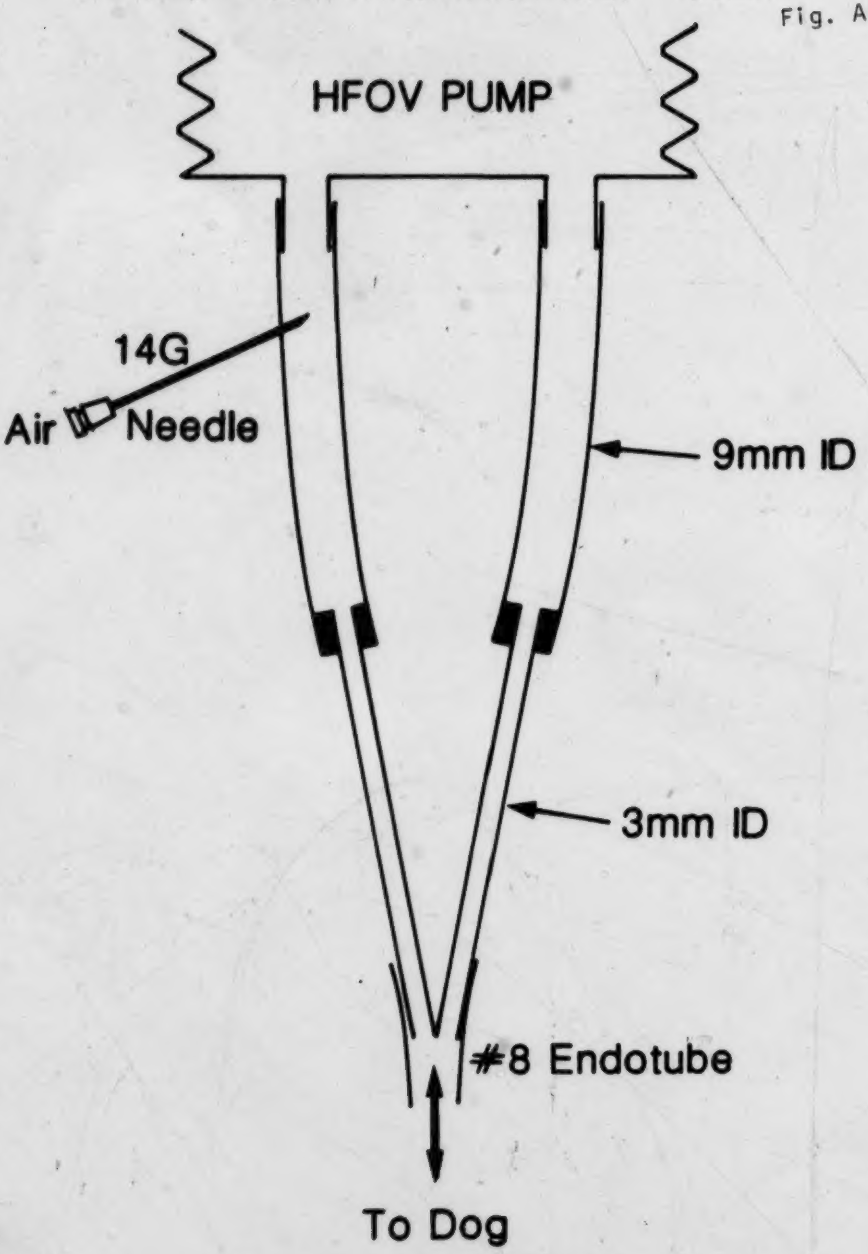

HFOV PUMP
14G
Air
Needle
9mm ID
3mm ID
#8 Endotube
To Dog

Figure AI-7: Basic HFOV circuit, final version.

Fig. AI-8

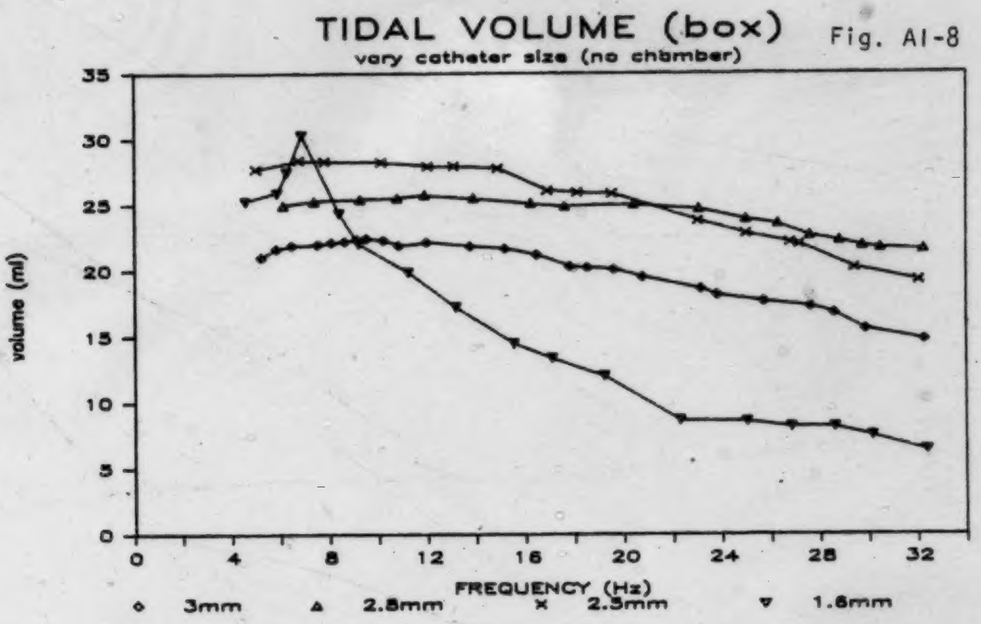


Fig. AI-9

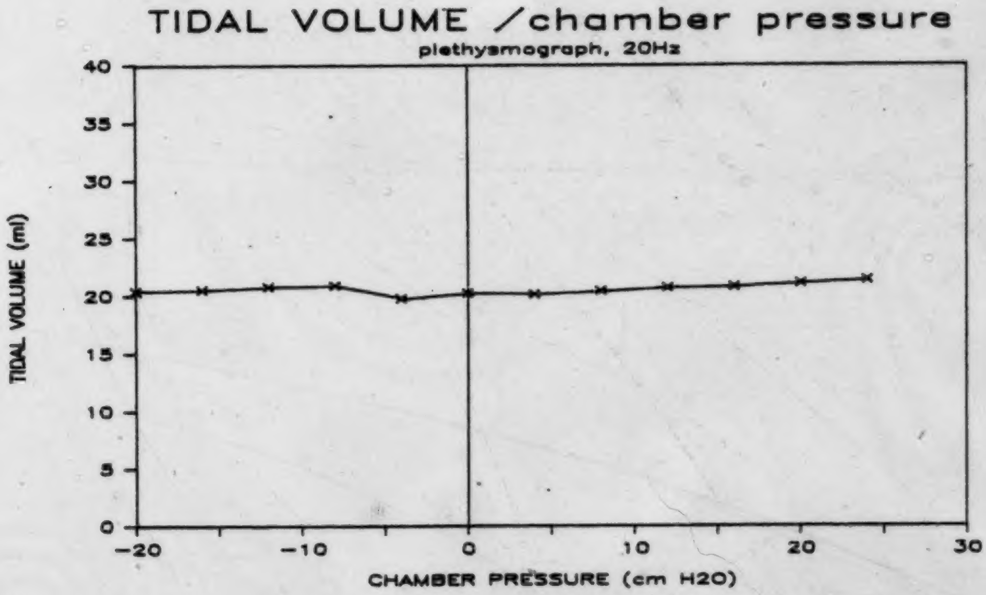


Figure AI-8: Tidal volume delivered by the HFOV pump through different-diameter catheters. Figure AI-9: Variation in tidal volume induced by changes in airway chamber pressure.

Fig. AI-10

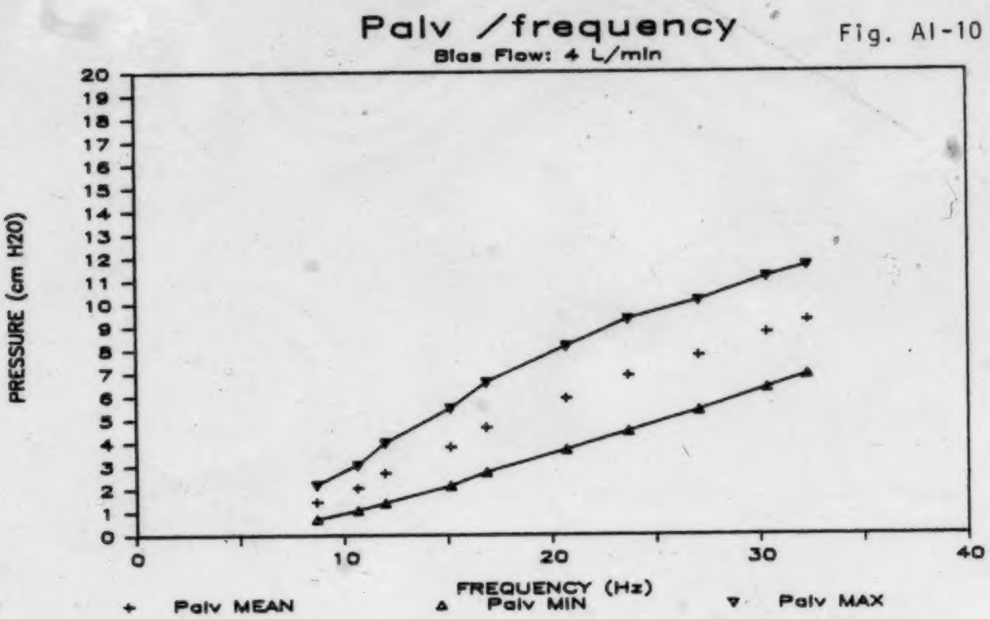
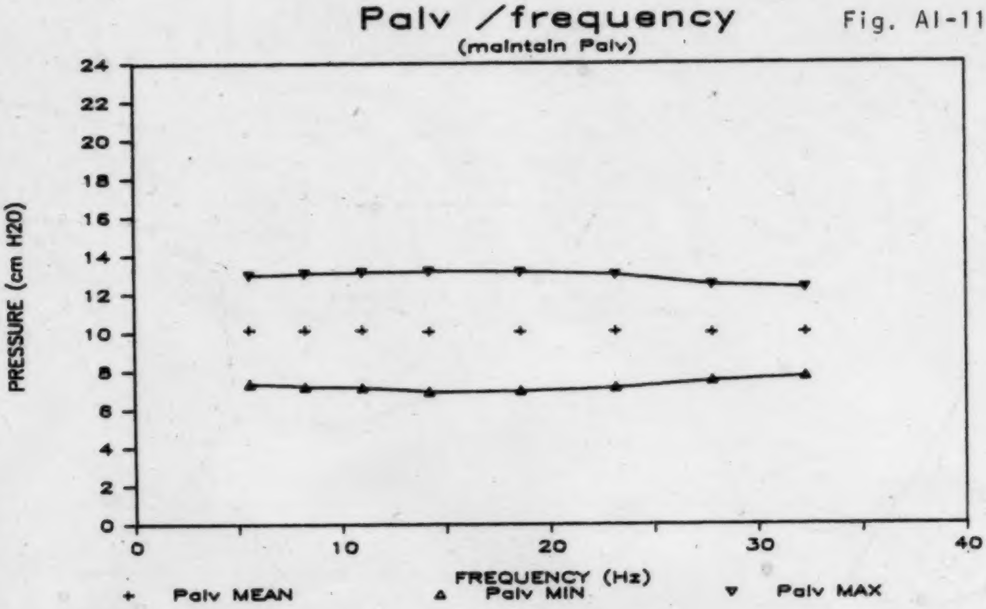


Fig. AI-11



Figures AI-10 and AI-11: Pressure developed in a lung model when HFOV frequency was increased without maintaining (top) and without maintaining (bottom) the model's internal pressure (Palv) stable.

Fig. AI-12

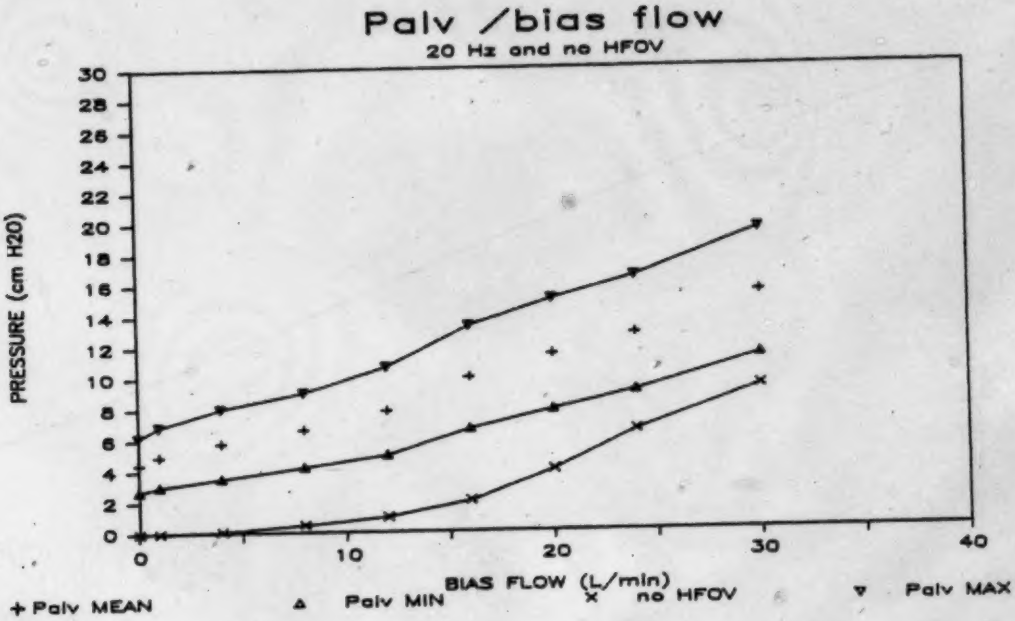


Figure AI-12: Change in lung model pressure (Palv) when bias flow was increased, with and without HFOV.

APPENDIX II

DEVELOPMENT OF THE BODY PLETHYSMOGRAPH

DESCRIPTION

The body plethysmograph used in the experiments described in this thesis was constructed out of Plexiglas 6.4 mm thick and had the following internal dimensions: length = 91.8 cm, width = 35.5 cm, height = 30.8 cm; the internal volume was 100 L. A plywood board (10 mm thick) that had two 15 mm thick strips of wood attached to its sides, was used to prevent the weight of the dogs from deforming the box floor (Fig.1, Chapter 4): weight was distributed by the wooden strips along the angle between the side walls and the floor of the box. The lid was also made out of Plexiglas (6.4 mm thick) and rested on a 50-mm wide Plexiglass frame attached to the top edge of the box walls. To create an airtight seal, an "O" ring made out of Neoprene (4 mm o.d.) and lubricated with silicone grease, was placed between the wall frame and the lid. Eight large steel clamps compressed the lid against the "O" ring, ensuring an airtight seal; the adequate compression of the Neoprene ring could be easily observed through the Plexiglas lid. With this setup, no air leaks could be detected when the box was pressurized up to 25 cm H_2O.

A steel rod (3 mm o.d.) passed through an airtight hole in the lid, at a position that corresponded to a mid-chest location of a dog placed inside the box; this rod was used as a plunger for external chest compression. The external end of the rod was screwed into an aluminum handle; at the other end, a 60-mm diameter rubber stopper was attached to distribute the compression pressure over a wide area of the dog's chest. When the plunger was not in use, a clamp prevented the rubber stopper from touching the dog's chest. A 6-mm thick aluminum angle bar was bolted to the outside of the lid at the location where the plunger entered the box, to prevent deformation during the compression maneuver. An appropriate metal spacing placed the aluminum bar's weight directly over the upper edge of the side walls of the box; this setup avoided any bending of the lid when the plunger was moved. The orifices where the plunger rod passed through the aluminum bar and box lid, were kept well lubricated to ensure airtightness and a smooth movement of the plunger. A 19 mm thick board was bolted to the box floor and rested on a sturdy metal frame. This frame was bolted to a wooden mobile cart which facilitated positioning of the box during the experiments.

Ten connectors were glued into the lateral walls of the box, to allow attachment of: arterial catheter, venous catheter, proximal and distal ports of the flow-directed catheter, left ventricular catheter, esophageal balloon, endotracheal tube cuff, etc. Three electrical plugs allowed connection of the cables for phrenic-nerve stimulation: right and left phrenic nerve, and ground (attached to a silver plate in contact with the dog's tongue); another electrical connector was used for attachment of the thermistor from the flow-directed catheter (used to measure $\dot{Q}$ and monitor core temperature). A large-bore connector (9 mm i.d.) with a 2-way stopcock allowed rapid equilibration of box pressure with atmosphere, or connection to a bell spirometer to monitor changes in volume (converting the box into a volume plethysmograph). A 3-mm i.d. connector was used to monitor box pressure with a Validyne MP45 transducer. The negative port of the transducer was attached to a 2 L bottle which had a controlled leak (20G needle); this system minimized the effect of ambient noise in Pbox. A 13-mm opening in one end of the box allowed a tight-fitting large-bore (9 mm i.d.) Silastic tubing (40 mm long) to connect the endotracheal tube from the inside of the box to the ventilator outside; a 3-mm i.d. connector on the side of the Silastic tubing was used to monitor $\overline{P}aw$. The elasticity of the Silastic tubing ensured airtight fitting and permitted clamping of the airway opening during FRC measurements. In some experiments, more openings were made in the wall of the Silastic tubing (and catheters secured with silastic glue) for Pd- and Ps-measuring catheters (Chapter 6).

For box calibration, a Plexiglas cylinder (diameter = 100 mm, length = 60 mm, inside volume = 476 ml) was attached to the inside of the box, just above the endotracheal tube connector. One end of the cylinder was sealed, the other was covered with a sheet of latex, which could be compressed from the outside with a small plunger (a 2-mm o.d. steel rod with a 1.3 mm rubber stopper at the tip). The cylinder contained a humidity absorber and was loosely packed with steel wool. A 2 mm i.d. plastic connector (35 mm long) could be attached to the Paw transducer, to monitor cylinder pressure during the box-calibration maneuver; at other times this connector remained occluded.

In preliminary trials it was found that once a dog had been placed inside the box, it took around 40 min to achieve box-temperature equilibration. All subsequent FRC measurements were performed when the dog had been inside the box for at least 1 h. In some long experiments, especially those involving large animals with long hair, the dog's core temperature showed a tendency to increase beyond physiologic levels. To bring the temperature to a normal range, an airtight plastic bag was placed on the animal's groin and connected to the outside of the box with plastic tubing. Repeated flushing of the bag with ice-cold water decreased the dog's temperature to the desired level. In some cases, especially in small dogs with short hair, core temperature had a tendency to decrease; hypothermia could be easily avoided by flushing the plastic-bag system with warm water.

DEVELOPMENT OF THE PLETHYSMOGRAPH

When the plethysmograph was first tested, it became evident that minor movements of its floor induced large noise artifacts in Pbox. This was corrected by bolting a thick board (19 mm) under the box, which rested on a sturdy metal frame. This setup was effective in minimizing artifacts due to box distortion. However, compression of the box floor with the large plunger still induced some Pbox fluctuations. It was decided to put another board inside the box with appropriate spacings along its sides, so the weight of the dog was distributed along the edges of the box. Compression of this board when it was in place, did not induce significant fluctuations in Pbox.

At first, it was decided to seal the lid with commercial putty, but this implied an elaborate process every time the lid had to be removed. It was decided to try a ring of Neoprene tubing greased with silicone compressed between the lid and the wall's frame by steel clamps. This system was finally adopted because it was clean, provided a good seal and allowed rapid lid removal.

In the initial design, the box included a 9-L temperature-compensation chamber to avoid fluctuations in Pbox due to temperature changes, and to decrease Pbox noise. However it was found that this system contributed significantly to looping in the X-Y tracings of Pbox vs Paw. An alternate system to decrease Pbox noise was then used, which included a sealed plastic bottle with a controlled leak connected to the negative port of the box transducer. To avoid temperature-induced fluctuations in Pbox, a 1-m piece of large bore tubing (12.7 mm i.d.) was connected to the pressure equilibration opening on the box wall (in the place of the 2-way stopcock). This allowed temperature equilibration of Pbox with minimal heat exchange when a dog was ventilated inside the box. To obtain FRC, this tubing was clamped immediately prior to the measurement; connection of this 1 m piece of tubing to a bell spirometer allowed the monitoring of lung volume fluctuations (due to ventilation or changes in FRC). When box temperature was equilibrated (the animal had been inside for at least 1 h), fluctuations in volume induced by temperature changes were minimal over a 3—4 min period.

In preliminary trials, Pbox and Paw were displayed on a photographic strip chart recorder (Electronics for Medicine model DR8), but baseline Pbox fluctuations and cardiac artifact (sometimes as large as 20% of the FRC-maneuver signal) made FRC calculation extremely difficult (and inaccurate). An X-Y recorder was subsequently used because the effect of cardiac artifact on the tracings was minimal, and baseline fluctuations could be easily corrected by manually positioning the pen. Also accuracy was enhanced because only one measurement had to be made (angle of the loop) instead of the two (Paw and Pbox) when using the strip chart recorder. The X-Y recorder was tested with a sine-wave generator (Hewlett Packard model 3300B), and its frequency response was found to be satisfactory for the FRC measurements (flat up to 3 Hz). At first, two different Validyne transducers were used (DP 109 for Pbox and MP45 for Paw), but it was found that a phase lag in their responses induced looping in the X-Y tracings; this was avoided by using two similar transducers (two Validyne MP45). The angle of X-Y recorder tracings was measured with a special ruler-goniometer (Faber-Castell model 1084, Germany) which allowed an accuracy on the readings close to ± 0.1 degrees (checked by trigonometry).

The initial calibration process was done as described by DuBois by injecting a known volume in the box (Pbox calibration) and calibrating Paw with a water manometer. This method was cumbersome and with several potential error factors. So the previously-described calibration chamber was designed, which permitted fast and accurate calibration (Appendix III), with few potential error factors.

In order to measure Raw as described by DuBois, a system was tested which consisted of a #1 Fleish. pneumotachograph placed inside the box and connected to a large side port in the ETT which in turn could be occluded from the outside. During ventilation or FRC measurement the pneumotachograph remained occluded. To measure Raw the airway was clamped at the outside of the box, and the pneumotachograph opened. Raw could then be calculated from the flow across the pneumotachograph and Pbox. However, the x-y tracings showed considerable looping (probably due mostly to water saturation and temperature changes) which precluded accurate readings. As the measurements of Raw were considered secondary and did not add much information, the system was not developed further.

APPENDIX III

COMPARISON OF VARIOUS PLETHISMOGRAPHIC METHODS FOR OBTAINING THORACIC GAS VOLUME IN ANESTHETIZED DOGS

INTRODUCTION

In the study of cardiorespiratory physiology, it is important to know the volume of the lungs. This measurement is useful in situations that require, for example, the assessment of the elastic characteristics of the respiratory system, the effects of artificial ventilation and positive end-expiratory pressure, the changes in pulmonary vascular resistances, the risk of small-airway closure, etc. The plethysmographic thoracic gas volume measurement described by DuBois (DUBOIS, A.B., S.Y. BOTELHO, G.N. BEDELL, R. MARSHALL, AND J.H. COMROE JR. J. Clin. Invest. 35: 322-326, 1956) has become a standard method for the assessment of lung volume. Basically, the subject breathes against an occluded airway and FRC is calculated from the resultant changes in box and mouth pressures applying Boyle's law. This requires an intact respiratory center to induce ventilatory movements. However, in the case of a profound inhibition of the respiratory center, breathing is delayed or even abolished and TGV can not be obtained in the usual manner. This situation is common in the research laborotory, for example during hypocapnia, deep anesthesia, high lung volume etc. In those instances, the pressure changes required in the Du Bois technique must be induced artificially. Two simple methods of plethysmographic TGV measurement in apneic animals are chest wall compression and phrenic nerve stimulation.

In this study, a plethysmograph was used to measure TGV in anesthetized dogs when the pressure changes were induced by: 1) spontaneous breathing, 2) external thoracic compression, and 3) bilateral phrenic nerve stimulation. The helium dilution method was used to measure ventilated lung volume. The external compression method gave higher TGV values, and to rule out a technical error, a mechanical lung model and isolated dog lung lobes were also studied. A simplified method for plethysmographic calibration is also described.

MATERI[illegible] AND METHODS

The plethysmograph: A 100 liter box was constructed with 6.4 mm thick Plexiglass (Fig AIII-1) with an airtight removable lid. To prevent the weight of the dog from deforming the floor of the box during the thoracic compression maneuver, the animals were placed on a board (10 mm thick) attached to the side walls and suspended 15 mm from the box floor. A metal rod (3 mm o.d.) with a 60 mm diameter rubber stopper at the tip, passed through an air tight orifice in the lid and acted as a plunger to compress the chest wall, lung model or isolated lobe. The lid was reinforced to prevent deformation during the compression maneuver. Several openings on the box walls allowed for the endotracheal tube, arterial and venous catheters, and phrenic nerve electrode cables to be connected to the outside. Box and mouth pressures (Pbox and Paw, respectively) were monitored with Validyne MP45 transducers, their outputs amplifed and fed into an X-Y recorder (model 815, MFE Corp., Salem, NH).

The calibration chamber: A Plexiglass cylinder (diameter = 100 mm, length = 60 mm) with one end sealed and the other covered with a sheet of latex, was attached to a wall of the box (Fig.AIII-1). The airway pressure transducer could be connected to the inside of the cylinder and a small plunger leading to the outside of the box was used to compress the cylinder's latex membrane. The calibration chamber was loosely packed with steel wool and contained a humidity absorber. The air-volume of the chamber was 476 ml.

Calibration: To calibrate the box, the endotracheal tube was occluded (with the dog, lung model or isolated lobe inside the box) and the chamber membrane was repeatedly compressed with the small plunger (moved by hand) to create changes in box and "airway" pressures which were displayed on the X-Y recorder (Pbox: X axis; Paw: Y axis). The compressions were performed at a rate of around 1 per sec). The recorder gains were adjusted to give an angle of approximately 45°. The angles (αcal) of at least five of these tracings were measured with a ruler goniometer (Faber-Castell model 1084-1094ZK, Germany) and their average used to calculate the calibration factor (Fcal) by the formula:

$$\text{Fcal} = (476 \times \tan \alpha\text{cal})/\text{Barometric Pressure}$$

which is a modification of the DuBois formula. Fcal was used to calculate TGV, as described below.

In vitro experiments with a lung model

A model of the lungs, consisting of two collapsible plastic bottles (Fig. AIII-2) attached to the endotracheal tube connector with a Y-piece, was placed in the box. The bottoms of both bottles were removed and replaced by a sheet of latex which could be pulled simultaneously from the outside of the box with strings to simulate diaphragmatic contraction. The two bottles were placed one on top of the other, under the box lid plunger to allow their simulateous compression, to simulate thoracic compression. The bottles were filled with steel wool and contained a humidity absorber. The total internal gas volume of the lung model was 548 ml and could be decreased by adding glass beads.

To simulate a TGV measurement by phrenic nerve stimulation, the latex membranes were pulled simultaneously while the endotracheal tube was occluded. This created changes in box and "airway" pressures which were displayed on the X-Y recorder. The slopes (α) of at least four tracings were measured as described earlier and their average used to calculate the lung model volume with the formula:

Vol = (Barometric Pressure/tang α) x Fcal.

which is also a modification of DuBois formula. The same formula was used to obtain the model volume during external compression, but in this case the "airway" pressure changes were induced by manually compressing the bottles with the lid plunger at a frequency of around 1 per sec. The bottles were partially filled with known volumes of glass beads and measurements by external compression and simulated phrenic nerve stimulation were repeated at six different lung model volumes.

Measurements in isolated lung lobes by external compression

Seven freshly excised dog lung lobes were used for these experiments. The lobe was placed inside the plethysmograph and the main airway was tied to a plastic tube attached to the endotracheal tube connector. The lobe was partially inflated and the airway occluded. The pleural surface was then manually compressed with the lid plunger at a rate of around 1 per s and the airway and box pressure changes were used to calculate the lobe volume as described for the lung model. In this case water vapour pressure was subtracted from barometric pressure. After the measurement, the anatomical airway was clamped and the volume of the lobe and tubing was obtained by water displacement. The gas volume of the lobe was taken as the volume (ml) of water displaced minus the lobe weight (g). The lobe was inflated to a different volume and the above procedure repeated. A total of 18 measurements were performed on the 7 lung lobes.

In vivo experiments

Eight mongrel dogs (8.9±2.4 kg) were anesthetized with intravenous pentobarbial (30 mg/kg), intubated with a cuffed endotracheal tube (9 mm o.d.), and ventilated with a Harvard respirator (Model 605) set at 15 breaths/min and a tidal volume of 15 ml/kg. A femoral artery catheter was used to obtain samples for blood gas analysis (Instrumentation Laboratory, model 813). A femoral vein catheter was used to maintain anesthesia and infuse a 3.3% glucose solution in 0.3% saline at a rate of 4 ml/kg/hr. Both phrenic nerves were dissected at the lower neck level, and connected to a Grass stimulator (Model SD9) with flexible metal electrodes. When preparation was completed, the animals were placed inside the plethysmograph in the left lateral decubitus position. During the hour allowed for box temperature equilibration. four lung volume measurements were made by the closed-circuit helium-dilution technique (HEWLETT, A.M., G.H. HULANDS, J.F. NUNN, AND K.B. MINTY. Br. J. Anaesth. 46: 479-485, 1974). The circuit used is shown in Fig. AIII-3. It consisted of a Harvard respirator (Model 605), a 9 liter bell spirometer (Collins model 6001) and a small fan to speed gas mixing. Helium concentration was measured with a Godart analyzer (Model PA44A2) and the output was amplified and displayed on a digital voltmeter (Hewlett Packard model 3430A). Two 3-way stopcocks allowed rapid connection of the respirator to the closed circuit or to ambient air. The spirometer contained a CO_2-absorbing canister, and oxygen could be added to the circuit to compensate for the dog's O_2 consumption. The total internal volume of the circuit was 2652 ml and the internal volume of the respirator with its tubings, in the end-expiratory position, was 1149 ml.

After completing 4 helium-dilution lung volume measurements, the three types of plethysmographic TGV measurements were made, their order assigned at random: spontaneous breathing, external compression and phrenic nerve stimulation.

TGV measurement by spontaneous breathing (TGV-SB) A few minutes before starting these measurements, the respirator rate was decreased to 11–12 bpm to increase $PaCO_2$ slightly and shorten the apneic periods. The dog's endotracheal tube connection was clamped at end- expiration and the changes in box and mouth pressures obtained during spontaneous respiratory efforts were registered on the X-Y recorder. The TGV was calculated as described for the isolated lobes.

TGV measurement by external compression (TGV-EC) For these measurements, the respirator was stopped at end-expiration, the airway occluded and the lateral chest wall compressed by hand with the plunger at a rate of around 1 per s. As the dogs were hypocapnic, spontaneous breathing did not occur during the time necessary to obtain the X-Y tracings (less than 30 s). In preliminary trials we found that compression of the lateral chest wall induced much larger pressure fluctuations than compressing the sternum in the supine position, thus improving the signal-to-noise ratio. A plunger displacement of 1 to 3 cm was necessary to induce a satisfactory pressure/volume change. This created local pressure at the chest wall/plunger interface that ranged between 12 and 25cm H_2O (measured with a waffer-like pressure sensor). The calculations involved were the same as previously described for the isolated lobes.

TGV measurement by phrenic nerve stimulation (TGV-PhN) For these measurements, the changes in thoracic volume after airway occlusion were produced by stimulation of both phrenic nerves with the Grass stimulator. This was done with pulses of 2 miliseconds duration, at a frequency of 40 to 60 Hz. The pulse voltage was varied manually from a level below threshold to above it, creating a progressive diaphragmatic contraction with a duration of around 1 s. The TGV-PhN was calculated from the X-Y tracings as described before.

During all these procedures, the dog's temperature was monitored, and kept at a physiologic level with a heating-cooling blanket system. Also, the lungs were hyperinflated to twice the tidal volume every 15-20 min and immediately before the TGV measurements to prevent atelectasis.

Statistical analysis of the data was performed with a paired t-test with a significance level at $p < 0.05$.

RESULTS

In vitro experiments, lung model: The actual volumes of the lung model were not statistically different from values obtained by external compression or simulated diaphragmatic contraction, and these two methods were also not significantly different from each other (Fig. AIII-4a).

Isolated lung: The 18 measurements of lung lobe volume obtained by water displacement were not statistically different from the values measured by external compression (Fig. AIII-4b).

In vivo experiments: The data obtained from the in vivo experiments is presented in Table AIII-1 and the statistical analysis in Table AIII-2. The external compression technique gave TGV values significantly larger than the TGV obtained by phrenic-nerve stimulation, spontaneous breathing and the lung volume measured by helium dilution. The values obtained by the latter three methods were not statistically different from each other.

DISCUSSION

Calibration of a body plethysmograph is usually accomplished by the separate calibration of the Paw transducer with a water manometer and the Pbox transducer with a known volume of air cycled in and out the plethysmograph by a syringe or piston pump. Calibration errors could result from: improperly reading the water manometer or in setting the pressure deflection on the X-Y recorder (or oscilloscope screen); an erroneous volume of the calibrating device; temperature induced changes in cycled volume; and reading the deflection on the recorder. There are, then, several potential sources of error in the standard calibration procedure.

In contrast, the method described in this paper has only two potential sources of error: measurement of the calibrating chamber volume and of the angle of the X-Y tracings. The chamber volume can be easily measured by water displacement and any error in the angle measurement can be minimized by averaging several tracings. The relatively slow frequency of chamber compression and the steel wool that filled the calibration chamber minimized the potential errors due to adiabatic compression (which would lead to overestimation of Paw and Fcal). Another advantage of this technique is the ease with which the calibration can be done: simply connect the Paw transducer to the calibration chamber port, occlude the airway and press the calibration plunger several times. This process takes less than a minute, compared to the several minutes required for the standard calibration.

The induction of inspiratory efforts by phrenic nerve stimulation allows TGV measurement in the research laboratory even when respiratory centre depression prevents the use of the standard spontaneous breathing technique. In situations like hyper-ventilation, deep anesthesia, high resting lung volume, or high frequency ventilation, the onset of breathing can be delayed leading to severe hypoxemia; in all those cases phrenic nerve stimulation can induce the diaphragmatic contraction required for TGV measurement. Very little equipment is needed: a pulse generator and a variable resistor. The electrodes used were made from small pieces of aluminum foil insulated from surrounding tissue with plastic tape. These electrodes worked well for acute experiments that lasted up to 20 hours.

In the in vivo experiments, TGV-PhN, TGV-SB and He-dilution lung volume gave comparable results. Differences between the He-dilution and plethysmographic techniques due to nonventilated air space would not be expected because sighs were often given during the experiments to prevent airway closure. In the experiments using a lung model with volumes in the range encountered in other in vivo experiments Chapter 2), both the simulated diaphragm contractions and external compression gave values that agreed well with the actual volumes of the model. Also, external compression of lung lobes gave results in agreement with their measured volumes. The lung model was filled with steel wool to avoid adiabatic pressure changes. Their presence during the experiments could not be ruled out, but the good correlation between actual and measured volumes indicates that the errors due to adiabatic phenomena (which would lead to overestimation of Paw and underestimation of the measured volume) were minimal. During EC of the lung lobes, the relatively slow speed of compression and large contact area provided by the airways and alveoli also minimzed errors due to adiabatic pressure changes. In the in vivo experiments, TGV-EC was significantly larger than TGV-PhN, TGV-SB, and He-dilution lung volume. Several precautions were taken to avoid artifacts during external compression: the lid was reinforced and the animals rested on a board which did not touch the box floor to avoid deformation during external compression. Compression of the board with the plunger was performed on an empty box, but no volume changes could be detected. A plunger volume of less than 0.3 ml was introduced into the box during external compression and this, if anything, would tend to underestimate TGV. The accuracy of lung lobe and lung model volume measurements by external compression support the idea that an artifact was not involved. Therefore, it can be postulated that external compression is an unsatisfactory method for TGV measurements *in vivo*.

In their original paper describing the EC technqiue, Avery and Sackner (AVERY, W.G., AND M.A. SACKNER. *J. Appl. Physiol.* 33: 515-518, 1972) found no significant difference between TGV-SB and TGV-EC values; however, actual data were not given. A major difference between the present method and that of Avery and Sackner was the size of the plunger shaft: the movement of their plunger during compression added approximately 1.91 ml to the box (calculated from Avery and Sackner diagrams) compared to 0.28 ml in this experiments. Using DuBois' formulas it can be calculated that for a Paw of 20 cm H_2O induced by compressing the chest of a dog with a TGV of 651 ml (Avery and Sackner's average), the introduction of 1.9 ml into the box would underestimate TGV by 14.5% (with a lower Paw the error would be even larger). Thus, the plunger probably caused a 14.5% underestimation of TGV-EC, but no difference was found between TGV-EC and TGV-SB. This suggests that if the plunger-related error had not been present in Avery and Sackner's experiments, their TGV-EC values would have been around 14.5% higher than TGV-SB. In the present study it was calculated that the plunger used causes TGV-EC to be underestimated by around 2.9%. This means that if the plunger-related error had not been present, TGV-EC values would have been 2.9% higher. The measured TGV-EC were already 8.8% above TGV-SB, and probably would have been 11.7% (8.8 + 2.9) higher if there were no plunger-related error. This 11.7% figure is similar to the previously-mentioned 14.5% difference calculated from Avery and Sackner's data. Consequently, it seems fair to speculate that although external compression leads to overestimation of TGV, the large volume of the plunger used by Avery and Sackner might have concealed it. Any variation in plunger shaft size or Paw changes would induce different errors in the method.

Although one cannot be certain of the cause for overestimation of TGV by external compression, it can be theorized that it could be due to intersegmental and interlobar volume shifts. The plunger compresses only a portion of the lateral chest wall and consequently alveolar pressure increases locally; alveoli in other parts of the lung being closer to atmospheric pressure, could receive volume from the compressed alveoli. Alveoli in the more compliant lung regions (like dependent segments) would be the most likely to expand during compression. During chest compesion abdominal volume increased, probably due to a downward diaphragmatic movement suggesting the basal lung regions were expanding. If intersegmental volume shifts did occur, one would expect some pressure to be lost in overcoming airway resistance, and mouth pressure to underestimate alveolar pressure; this would induce an overestimation of the TGV. A similar mechanism has been advocated to explain the overestimation of plethysmographic TGV in asthmatics. During compression of isolated lobes, a large fraction of the pleural surface was compressed by the plunger, preventing major volume shifts.

TABLE AIII-1: Individual TGV measurements (ml/kg) obtained in vivo by the different methods. Values in parentheses are the dogs' weight.

Dog # (weight)	Phrenic-nerve stimulation	External compression	Spontaneous breathing	Helium dilution
1 (12.6 kg)	58.6	63.3	56.4	59.9
2 (7.7 kg)	54.01	55.1	52.2	52.9
3 (10.1 kg)	38.3	44.5	36.6	43.0
4 (8.9 kg)	63.9	66.6	63.3	63.3
5 (7.3 kg)	51.4	55.8	57.3	51.1
6 (10.9 kg)	39.9	43.6	40.6	40.6
7 (9.0 kg)	36.4	42.9	34.2	39.9
8 (4.6 kg)	44.8	46.5	43.9	42.4
average ± SD:	48.4 ± 10.1	52.3 ± 9.3	48.1 ± 10.7	49.1 ± 9.1

TABLE AIII-2: Statistical analysis of differences in TGV measured in the in vivo experiments (mean ± SD).

Comparison	Differences (ml/kg)	t value	p significance
EC-PhN	3.88 ± 1.97	5.571	<0.001
EC-SB	4.22 ± 3.39	3.530	<0.01
EC-He	3.15 ± 1.00	8.872	<0.001
PhN-SB	0.35 ± 2.71	0.366	>0.05
PhN-He	-0.73 ± 2.38	0.771	>0.05
SB-He	-1.08 ± 4.10	0.862	>0.05

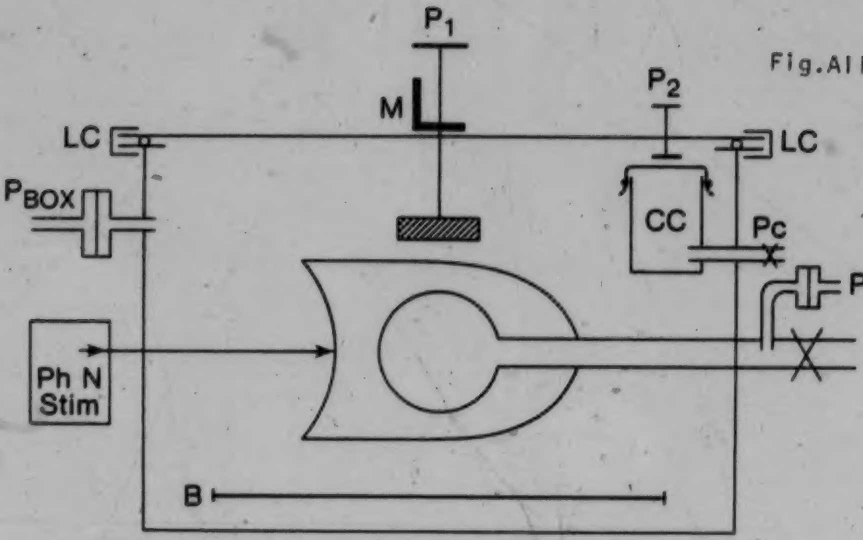


Fig.AIII-1

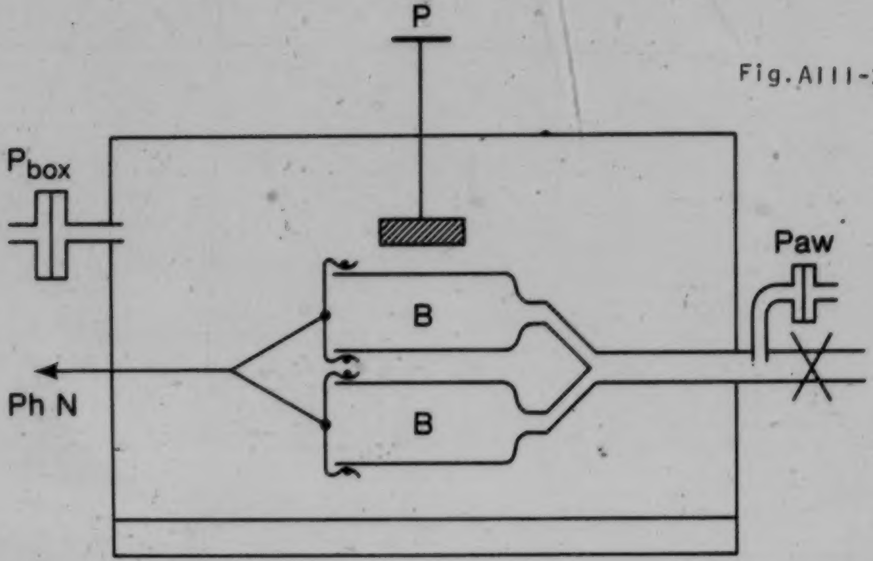


Fig.AIII-2

Figure AIII-1: Diagram of the plethysmograph. B, floor board; CC, calibration chamber; LC, lid clamp; M, metal bar attached to the lid; P_1, chest compression plunger; P_2, calibration chamber plunger; Paw, airway pressure transducer; P_{BOX}, box pressure transducer; Pc, calibration chamber pressure port; PhN Stim, phrenic nerve stimulator.Figure AIII-2: Diagram of the lung model setup. P, compression plunger; Paw, P_{BOX}, airway and box pressure transducer; PhN, strings to simulate diaphragm contraction; B, plastic bottles.

Fig.AIII-3

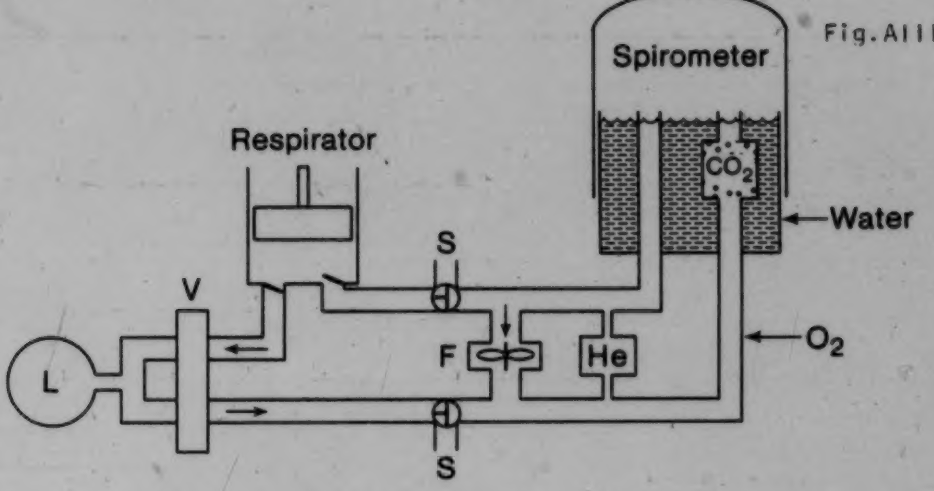


Fig.AIII-4

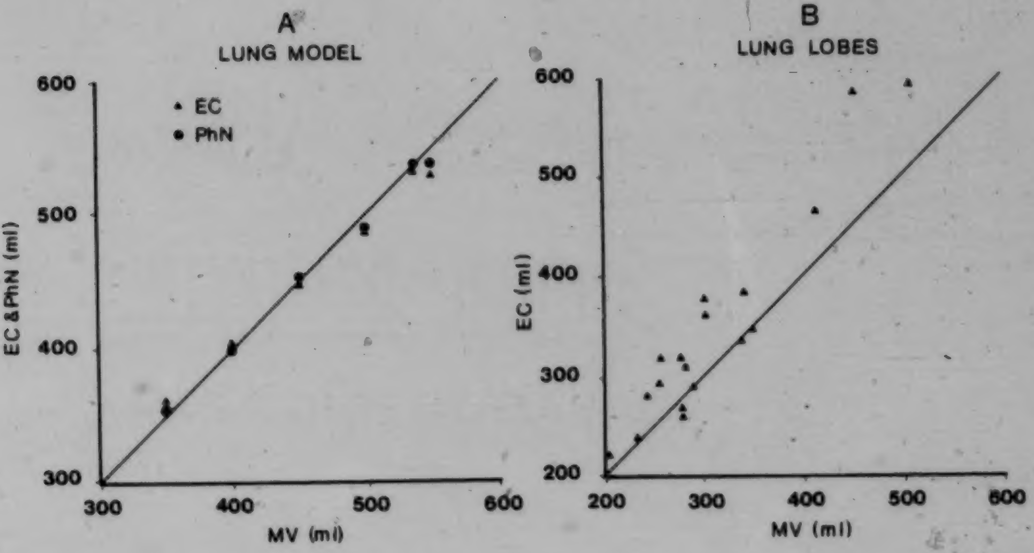


Figure AIII-3: Helium dilution circuit diagram. CO_2, carbon dioxide absorber; F, fan; He, helium analyzer; L, lung; O_2, oxygen flow; S, three way stopcock; V, respirator valves. Figure AIII-4.Lung model volumes measured by external compression (EC) and "phrenic nerve stimulation" (PhN) compared to actual volumes (MV). Also shown are isolated lobe volumes measured by external compression (EC) compared to volumes measured by water displacement (MV).

APPENDIX IV

CHANGES IN HEMODYNAMICS, LUNG MECHANICS AND GAS EXCHANGE IN DOGS WITH SALINE-LAVAGED LUNGS

INTRODUCTION

In previous chapters the effects of HFOV on cardiovascular function and lung mechanics have been characterized. In preliminary trials (Chapter 9F) it was found that dogs with oleic acid-induced pulmonary edema were difficult to ventilate with HFOV, probably due to damage to both lung parenchyma and the pulmonary circulation as well as to fluid accumulation in the interstitium, alveoli and airways. In order to investigate the effects of HFOV on $\bar{V}_L$ and Cst, an attempt was made to develop a lung injury model in the dog that would more selectively affect lung mechanics, inducing less hemodynamic changes and less fluid accumulation in the airways. The surfactant-depletion model induced by saline lavage has been described in the guinea pig and rabbit (see Introduction), and seemed to be a reasonable choice. In the present experiments, the effects of saline lavage of dogs lungs on Cst, gas exchange and basic hemodynamic parameters are described.

MATERIAL AND METHODS

Six mongrel dogs (9.2 ± 1.9 kg) were anesthetized with pentobarbital (30 mg/kg), intubated with a 9 mm i.d. ETT and ventilated with a Harvard respirator (model 607) at 15 bpm and V_T of 15 ml/kg. A catheter was inserted in the femoral artery to obtain samples for blood gas analysis (Instrumentation Laboratories analyzer model 813); a 7F flow-directed catheter was introduced in the pulmonary artery (through the femoral vein) to obtain $\overline{PAP}$ and PWP (Statham P23Db); a polyethelene catheter (PE90) was placed in the left ventricle (through the femoral artery) to measure LVEDP, left ventricular systolic pressure (LVSP), and left ventricular dP/dt (Statham P50 transducer and Gould Pressure

Processor model 13-4615-52). A differential pressure transducer (Validyne model MP45) was used to monitor Paw at the proximal ETT level; a similar transducer was used to monitor Peso from a esophageal balloon (length 5.0 cm, diameter 1.8 cm) situated in the lower-third of the esophagus. A solution of 3% dextrose in 0.3% saline was infused through the proximal port of the flow-directed catheter at a rate of 0.5 ml/kg/h; anesthesia was maintained through the same catheter, with boluses of pentobarbital, as required.

Calibration of the esophageal balloon: Before insertion, the esophageal balloon was calibrated by bringing its inside pressure to -30 cm H_2O and then injecting known volumes of air while the pressure was being monitored. The volume that brought pressure to 0 cm H_2O was called minimal inflating volume and was usually close to 1.5 ml (Fig.AIV-1). Once the balloon had been positioned in the lower third of the dog's esophagus, and a warm-up period had elapsed (20--25 min), the balloon pressure was brought to -30 cm H_2O, an amount of air equal to the minimal inflating volume was injected and the transducer connected to the balloon catheter for the rest of the experiment.

Constructing P/V curves of the lungs: To assess Cst of the lungs static P/V curves were obtained as follows: a large calibrated syringe was connected to the ETT and Paw raised rapidly to around 30 cm H_2O, three consecutive times; the airway was then opened to the atmosphere for 5--7 s to allow the lungs to reach FRC. Subsequently the syringe was reconnected and known volumes of air in 5--8 increments (of 100 ml) were injected every 3--4 s; the same volumes were then withdrawn at similar speed. The P/V curves were constructed by plotting the volume changes on the Y axis and transpulmonary pressure (P_L = Paw - Peso, subtracted electronically) on the X axis. Resting lung volumes were not available to plot absolute volumes in the Y axis. Compliance was obtained from the slope of the linear regression equation fitting the 4 lower points of the deflation limb of the P/V curve.

Lung lavage: To lavage the lungs, the animals were first ventilated with 100% O_2 and PEEP of 3 cm H_2O for 20 min (for the last 5 min the respiratory rate was increased to 20 bpm), and then placed in the left lateral decubitus position with the operating table slightly tilted to leave the head in a dependent position. The ETT was connected to a funnel kept at 30 cm above mid-chest level, and 40 ml/kg of saline at 37° were poured into the lungs as quickly as possible. The chest and abdomen were shaken gently to facilitate the replacement of lung gas by saline. When the flow of saline into the lungs had ceased, the ETT was disconnected from the funnel tubing, and its tip positioned below the level of the operating table to allow the saline to drain out of the lungs (an appropriate container gathered all the fluid). When most of the fluid had drained, the chest and abdomen were squeezed gently to help remove residual fluid; when the flow of fluid had ceased, the animal was reconnected to the respirator (the apnea period lasted around 60 s). To further remove lavage fluid from the lungs, during the first 8—10 mechanical breaths, a large port situated at the endotube connector was suddenly opened to atmosphere at end inspiration to create a sudden high expiratory flow that would remove fluid from large airways. After three minutes the lavage was repeated, for a total of 6 times; the animal was placed then on a right lateral decubitus position and 6 more lavages performed. The total volume of lavage fluid recovered from the lungs was subtracted from the volume of saline instilled, to obtain the amount of retained fluid. Samples from the 1st, 6th and 12th lvages were analyzed for total protein content (Folin method) and albumin (electrophoresis).

Experimental protocol: During the preparation period, the animals were ventilated with room air, and a PEEP of 3 cm H_2O to prevent anesthesia-related atelectasis. When the preparation was finished, the animals were ventilated with IPPV, 15 bpm and a V_T adjusted to induce a $PaCO_2$ of 30 ± 4 torr (assessed by arterial blood gas analysis). Fifteen minutes later an arterial sample was withdrawn for baseline blood gases, hemodynamic parameters were measured and a P/V curve was obtained. The animals were then ventilated for 20 min at 3 cm H_2O of PEEP and 100% O_2, and the lavage performed as described above. After the lavage, the animals were placed in a supine position and ventilated with IPPV and 100% O_2 for 60 min (in preliminary trials it was found that this IPPV period was necessary to induce a "stable" lung damage); blood gas analysis, P/V curve and hemodynamic measurements were performed 30 and 60 min after the lavage period. The animals were then ventilated at 3 cm H_2O of PEEP for 4 more hours, with blood gases, P/V curves and hemodynamic measurements obtained at hourly intervals. At the end of the experiment the animal was sacrificed and the chest opened to examine macroscopically the lung surface. $P(A-a)O_2$ was obtained with the standard alveolar air equation assuming an R value of 0.8.

Statistical analysis: The overall effect of time after lavage on different parameters was tested with a 2-way analysis of variance (ANOVA) and differences between time periods with a Duncan's new multiple-range test. Post-lavage IPPV values were used only to monitor the evolution of the damage and were not included in the statistical analysis. Values are expressed as mean ± SD, and the significance level was set at $p<0.05$.

RESULTS

The volume retained in the lungs after the lavage averaged 27.8 ± 9.8 ml/kg (range 17.9 to 46.7) which was an average 5.8 ± 2.1% (range 3.7 to 9.7) of the total lavage fluid used. If all this fluid had been absorbed, the total amount of fluid received by the dogs over the entire experiment (estimated from lavage fluid retained, plus i.v. solution, plus catheter flushing) averaged 4.7 ml/kg/h. The average protein contents of lavage fluid from samples #1, 6 and 12, were respectively: 25.3 ± 15.8 mg/100 ml, 8.5 ± 3.8 mg/100 ml and 6.2 ± 2.5 mg/100 ml; the albumin contents were: 6.8 ± 5.9 mg/100 ml, 1.8 ± 0.7 mg/100 ml and 0.8 ± 0.4 mg/100 ml.

The average values of individual parameters obtained at different experimental periods is shown in Table AIV-1; F values of the ANOVA as well as signifcance levels of the Duncan's tests are included. The IPPV values obtained 0.5 and 1 h after lavage were usually situated between the control and PEEP values; they were not compared statistically to control or PEEP measurements, and will not be discussed further in this section. After lavage there was a significant drop in Cst that remained stable for the observed periods thereafter (Figs. AIV-2 and AIV-3); it was accompanied by an opposite change in $\bar{P}$aw (Fig.AIV-4). $\bar{P}$eso decreased after lavage, the values at hours 3—5 were significantly different from control levels, but not the measurements at hour 2 (Fig.AIV-5); the second hour was similar to hour 3 ($p>0.05$), but different from hour 4 ($p<0.05$) and hour 5 ($p<0.01$). $\bar{P}_L$ increased sharply after lavage and continued to rise slightly thereafter (Fig.AIV-6). The control PaO_2 values were obtained while the animals were ventilated with room air and subsequent measurements were made while on 100% O_2, consequently the ANOVA included only PEEP data. After lavage, mean PaO_2 was near 100 torr (Fig.AIV-7) despite ventilation with 100% O_2, because of a large increase in $P(A-a)O_2$ (Fig.AIV-8); both parameters remained stable throughout the PEEP period. The large SD's obtained are mostly due to data from dog 3, which maintained a low $P(A-a)O_2$ throughout the experiment. $PaCO_2$ increased significantly after lavage, and remained stable during the PEEP periods (Fig.AIV-9). $\overline{PAP}$ increased slightly with time (Fig.AIV-10) but the overall differences were not significant (ANOVA's F: $p>0.05$) and only the 5th h value was higher than control (Duncan's $p<0.05$). A small and non-significant decrease in PWP (Fig.AIV-11) and LVEDP (Fig.AIV-12) was observed, the gradients PWP-LVEDP remaining quite stable (Fig.AIV-13). Minor and non-significant changes were observed in LVSP (Fig.AI-14) and dP/dt.

Postmortem examination of the pleural surface of the lungs showed consolidated areas of purple coloration in dependent regions, areas of red coloration in the middle regions and normal-looking uppermost lung regions. The extent of damage in each of these regions varied between 20 and 50% of the pleural surface.

DISUCUSSION

The details of this protocol were developed after several preliminary trials. From these, the following conclusions were drawn: a large amount of fluid (80 ml/kg) lavaged into a supine dog induces severe hypoxia and hypotension; lavaging in a lateral decubitus position reduces the hypoxia; previous ventilation with 100% O_2 also reduces the hypoxia; ventilation with PEEP immediately after the lavage, progressively improves the lung lesion (Cst and PaO_2 increase with time); ventilation without PEEP immediately after the lavage has the opposite effect; ventilation with 3 cm H_2O of PEEP after 1 h on IPPV induces a lung lesion stable for several hours (as assessed by Cst and PaO_2).

In the present experiments, care was taken to reduce the amount of saline retained by the lungs that, if absorbed, could cause fluid overload. The technique employed (with maneuvers like table tilting, chest and abdomen compression and end-inspiratory airway opening) was effective in removing most of the saline from the lungs: the amount of fluid recovered was always above 90% of the total. The retained saline was probably absorbed rapidly into the blood stream and could have overloaded the left ventricle, at least momentarily, however no high levels of PWP or LVEDP were detected. The total amount of fluid received by the dogs was not excessive, it averaged less than 5 ml/kg/h.

The fluid recovered from the lungs in the first few lavages was milky and contained many tiny bubbles, probably due to the presence of surface-active material. Later washings produced clearer fluid with fewer and larger bubbles, probably because less surface-active material was present; no measurements of surfactant-related compounds were made. The decreasing concentration of total protein and albumin indicated that less airway and/or alveolar lining fluid was being flushed out, and that a major disruption of the alveolo-capillary barrier was not induced during lavage. However several animals had pink frothy airway secretions in late stages of the experiments, which could have been related to alveolo-capillary membrane damage. The lack of surfactant could have facilitated widespread alveolar collapse with high critical opening pressure which could have induced overdistension of the open alveoli and damage to their walls. The increased surface tension could also have altered the alveolar fluid balance and induced interstitial fluid to move into the air spaces. All this indicates that the saline lavage model creates not only a stiff lung, but also some pulmonary edema. This fluid accumulation could have contributed, together with the alveolar collapse, to the high $P(A-a)O_2$ observed. The macroscopic appearance of the lungs, corresponded to a localized and probably gravity-related hemorrhagic pulmonary edema, which indicates that the lung damage was severe enough to allow passage of red cells into the air spaces.

The drop in Cst shows that the saline lavage was successful in inducing a stiff lung which remained quite stable during the period studied. However, $\bar{P}_L$ showed a slight tendency to increase with time (and $\overline{\text{P}}$eso to decrease), which probably indicates that the lungs were being ventilated on progressively more disadvantageous parts of the P/V curve, but without altering its overall slope (Cst). FRC values were not obtained in the present experiments for technical reasons; however, data from Chapter 5 suggest that FRC remained stable after the IPPV period post-lavage. The calculated $\bar{P}_L$ was obtained during dynamic conditions, and other factors besides the lung elastic recoil (like airway resistance and airway closure) were probably influencing the results. The Peso values were also an indirect index of Ppl and the relatively high levels observed could be a reflection of compression of the esophagus by mediastinal structures in a supine animal.

The stability of the hemodynamic parameters indicates that the saline-lavage model probably produces little cardiovascular impairment. Only $\overline{PAP}$ showed a slight but significant increase (Duncan's test) at the 5 h period, which could have been related to an increase in PVR induced by widespread alveolar (and capillary) collapse.

In conclusion, the present technique of saline lavage in the dog induces lung damage with decreased compliance and very little hemodynamic impairment. These observations also suggest that this procedure induces some degree of non-cardiogenic pulmonary edema.

TABLE AIV-1: Statistical analysis (ANOVA multiple range test and Duncan's) of parameters before (IPPV) and 2,3,4 and 5h (PEEP) after saline lavage of the lungs

	IPPV	PEEP 2h	PEEP 3h	PEEP 4h	PEEP 5h	F value
Cst (ml/cm H_2O)	43.8 ± 14.93	27.8 ± 11.1 **	24.7 ± 9.18 **	24.3 ± 9.82 **	23.4 ± 6.33 **	15.40 **
$\overline{P}$aw (cm H_2O)	3.82 ± 0.58	10.1 ± 1.58 **	10.3 ± 1.53 **	10.6 ± 1.55 **	10.8 ± 1.77 **	87.73 **
$\overline{P}$eso (cm H_2O)	2.00 ± 0.60	1.22 ± 1.04 NS	0.87 ± 1.21 *	0.23 ± 1.08 **	-0.17± 1.05 **	8.65 **
$\overline{P}_L$ (mmHg)	1.82 ± 0.96	8.92 ± 2.01 **	9.40 ± 1.80 **	10.4 ± 1.84 **	10.9 ± 2.13 **	71.98 **
PaO_2 (mmHg)	95.9 ± 4.83	134 ± 98.2 NS	132 ± 89.7 NS	156 ± 117 NS	135 ± 94.4 NS	1.33 NS
$P(A-a)O_2$ (mmHg)	12.8 ± 4.10	481 ± 96.9 NS	486 ± 88.9 NS	461 ± 115 NS	482 ± 94.6 NS	1.24 NS
$PaCO_2$ (mmHg)	30.0 ± 3.20	36.7 ± 3.52 **	34.6 ± 3.34 **	34.8 ± 3.08 **	34.8 ± 1.53 **	6.39 **
$\overline{PAP}$ (mmHg)	14.3 ± 3.16	15.3 ± 4.28 NS	15.8 ± 3.09 NS	16.8 ± 3.34 NS	18.2 ± 3.57 *	2.69 NS
PWP (mmHg)	6.03 ± 2.68	6.22 ± 1.71 NS	5.58 ± 1.90 NS	4.17 ± 1.80 NS	4.57 ± 2.32 NS	1.29 NS
LVEDP (mmHg)	3.03 ± 3.23	2.88 ± 1.75 NS	2.50 ± 2.00 NS	2.17 ± 2.23 NS	1.53 ± 1.38 NS	1.41 NS
LVSP (mmHg)	136 ± 21.8	127 ± 12.8 NS	124 ± 14.2 NS	125 ± 15.9 NS	129 ± 11.7 NS	0.75 NS
PWP-LVEDP (mmHg)	3.00 ± 1.97	3.33 ± 2.89 NS	3.08 ± 2.68 NS	2.00 ± 1.57 NS	3.03 ± 2.76 NS	0.96 NS
dP/dt (mmHg/sec)	45.9 ± 13.5	39.2 ± 10.1 NS	43.6 ± 12.6 NS	44.2 ± 8.55 NS	48.3 ± 10.6 NS	0.91 NS

Values are mean ± SD. NS: $p>0.05$; *: $0.05>p>0.01$; **: $p<0.01$

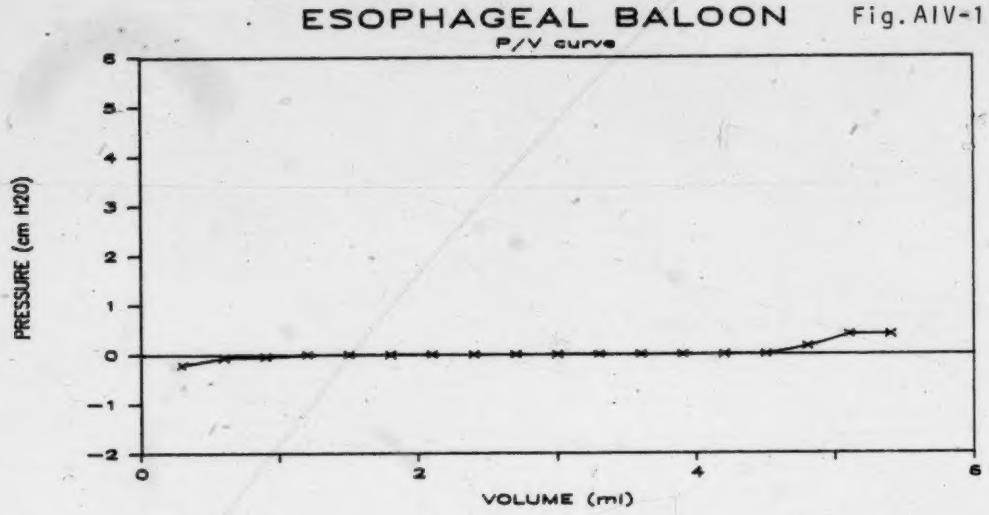


Fig. AIV-1

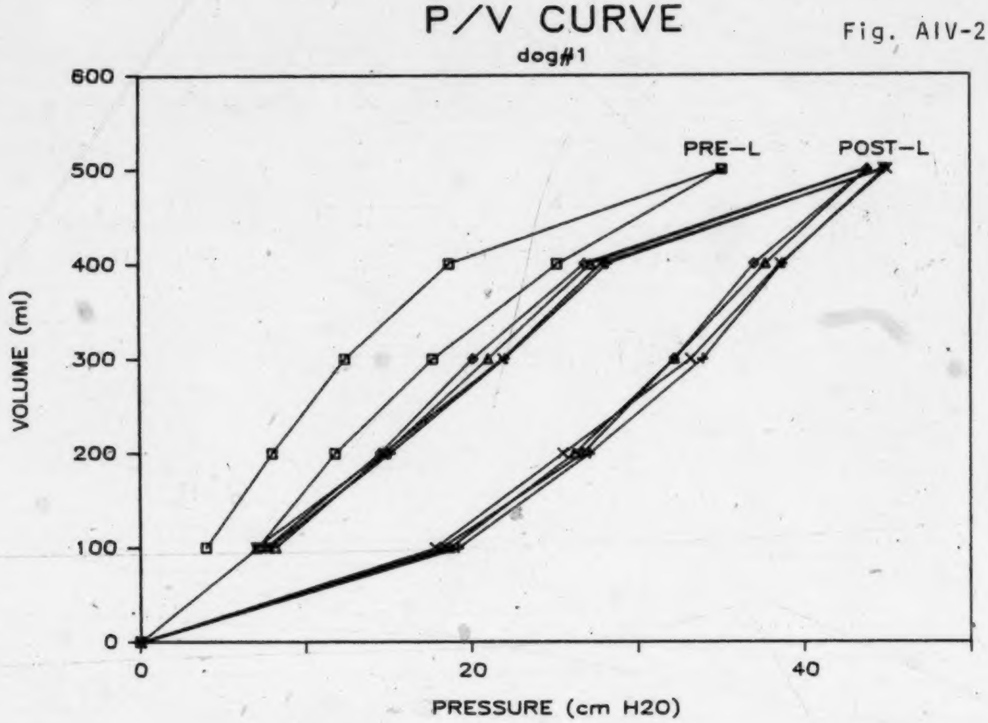


Fig. AIV-2

Figure AIV-1: Pressure/volume curve of the esophageal baloon. Figure AIV-2: Pressure/volume curve of one dog before and at 4 hourly intervals after lung lavage.

Fig. AIV-3

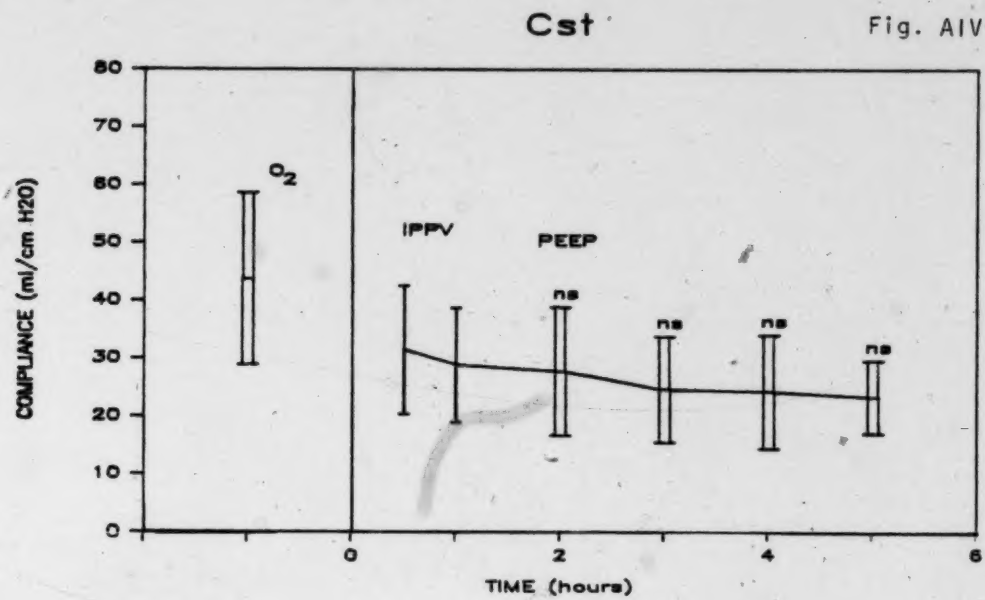
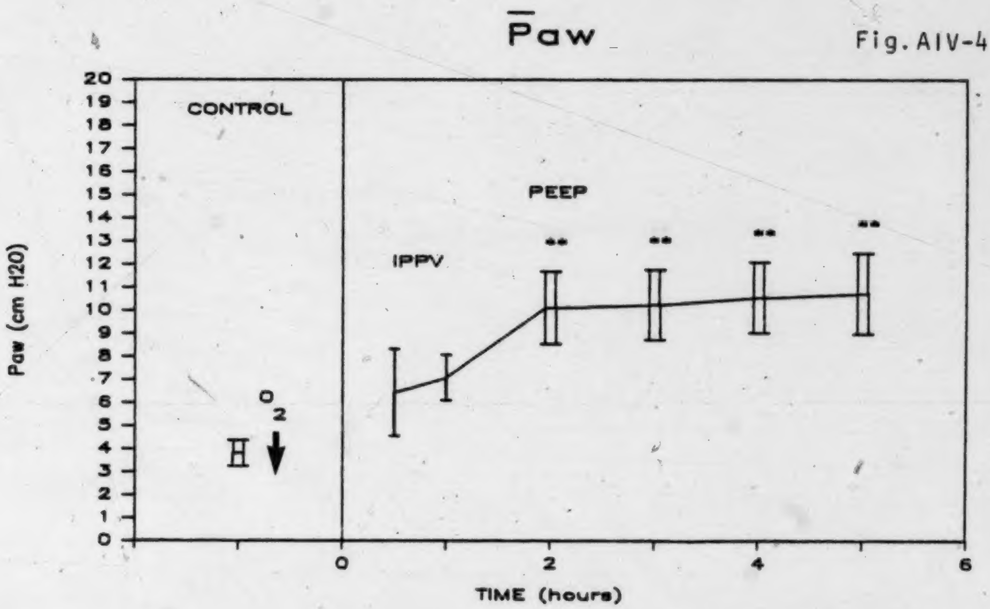


Fig. AIV-4



Figures AIV-3 and AIV-4: Average static deflation compliance (top) and mean airway pressure (bottom) changes before and after saline lavage of the lungs. Arrow, start $F_iO2=1$; ns, $p>0.05$; *, $0.05>p>0.01$; **, $p<0.01$.

Fig. AIV-5

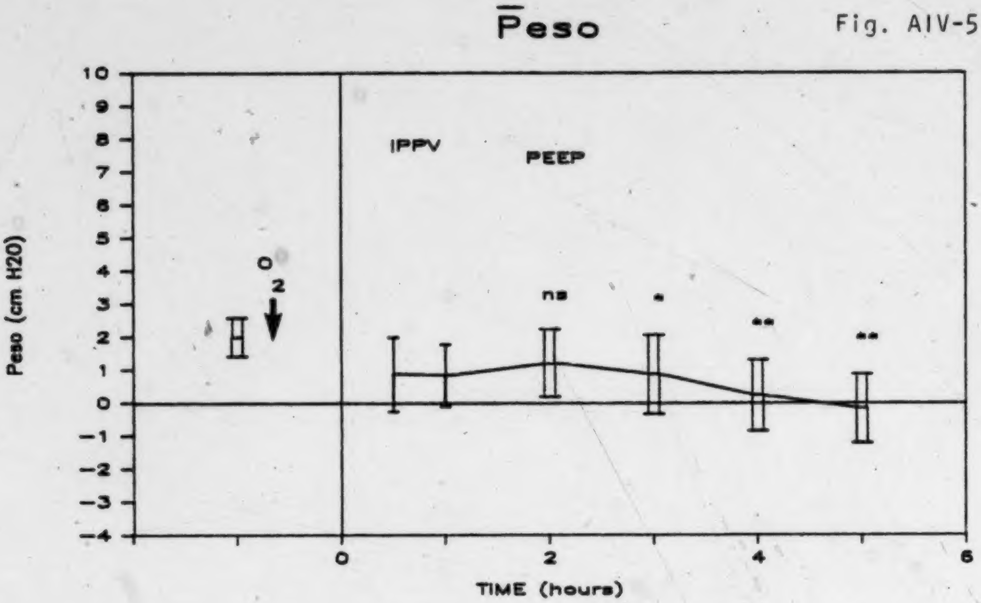
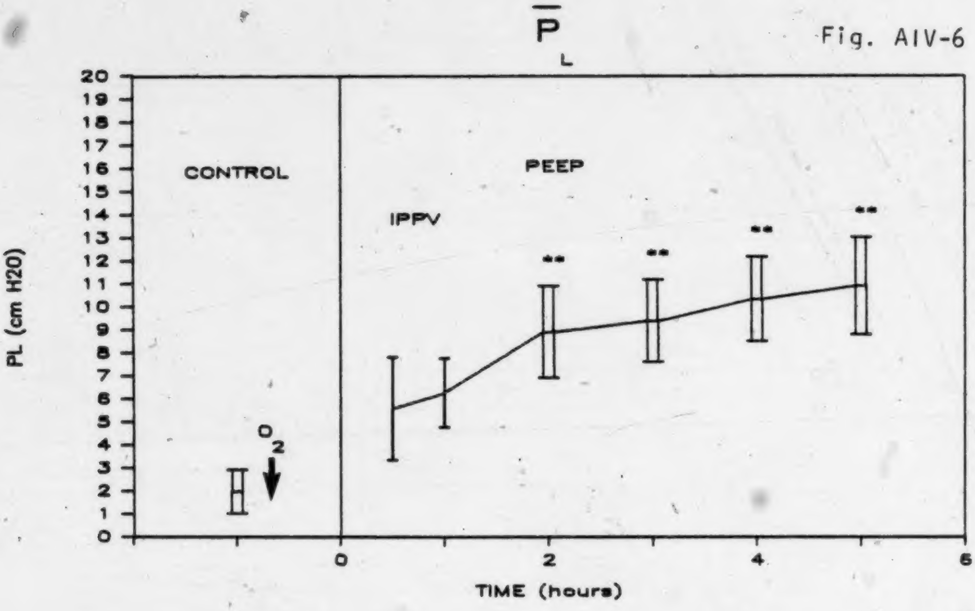


Fig. AIV-6



Figures AIV-5 and AIV-6: Average mean esophageal pressure (top) and mean transpulmonary pressure (bottom) changes before and after saline lavage of the lungs. Symbols as in Fig AIV-3.

Fig. AIV-7

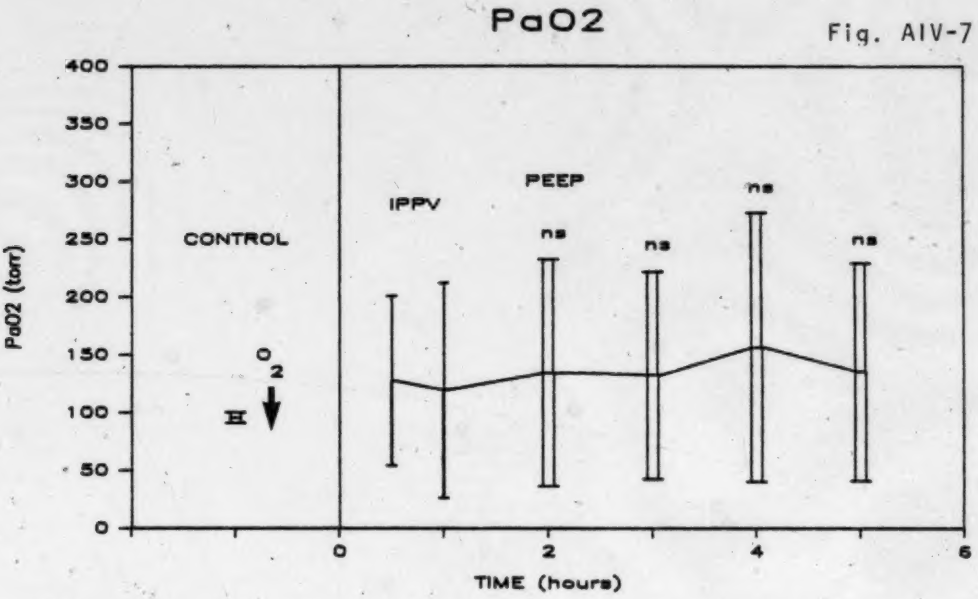
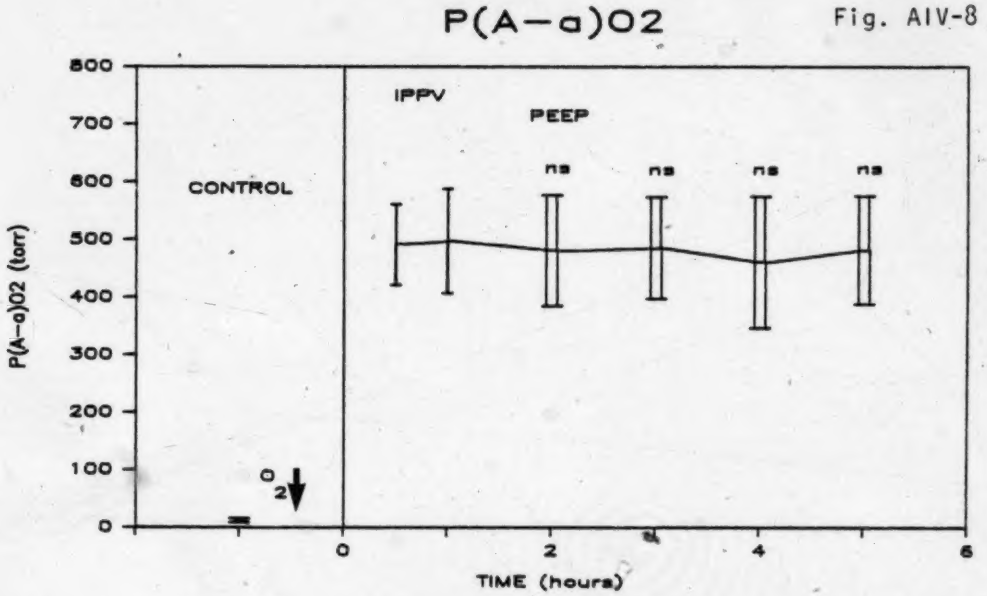
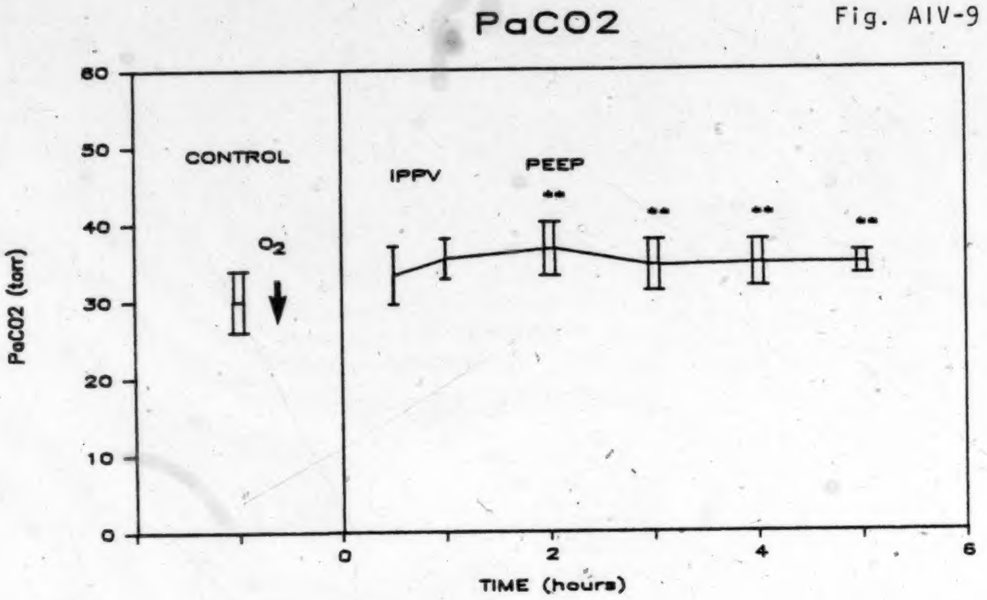
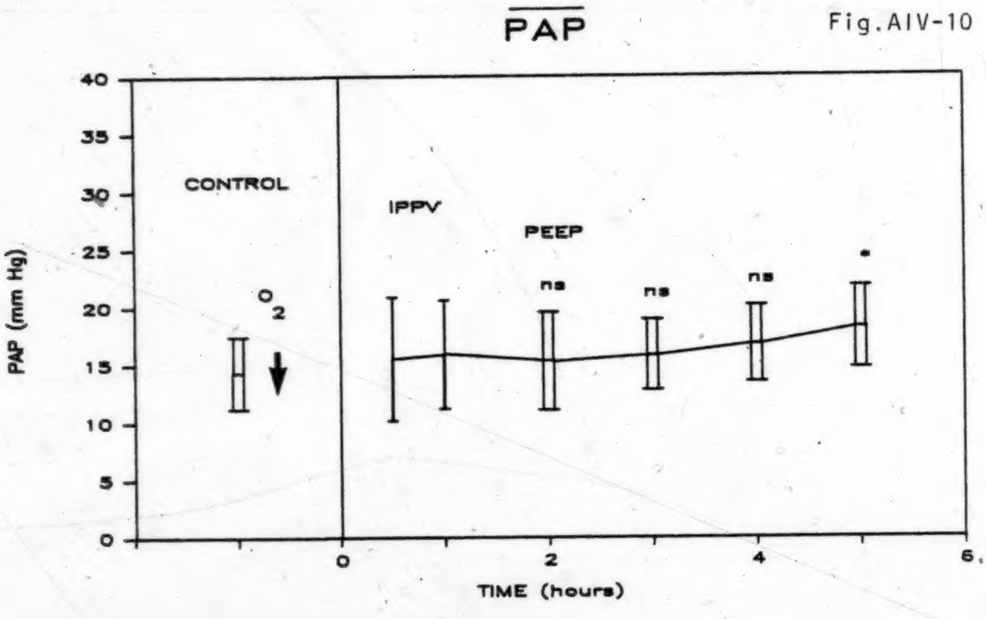


Fig. AIV-8

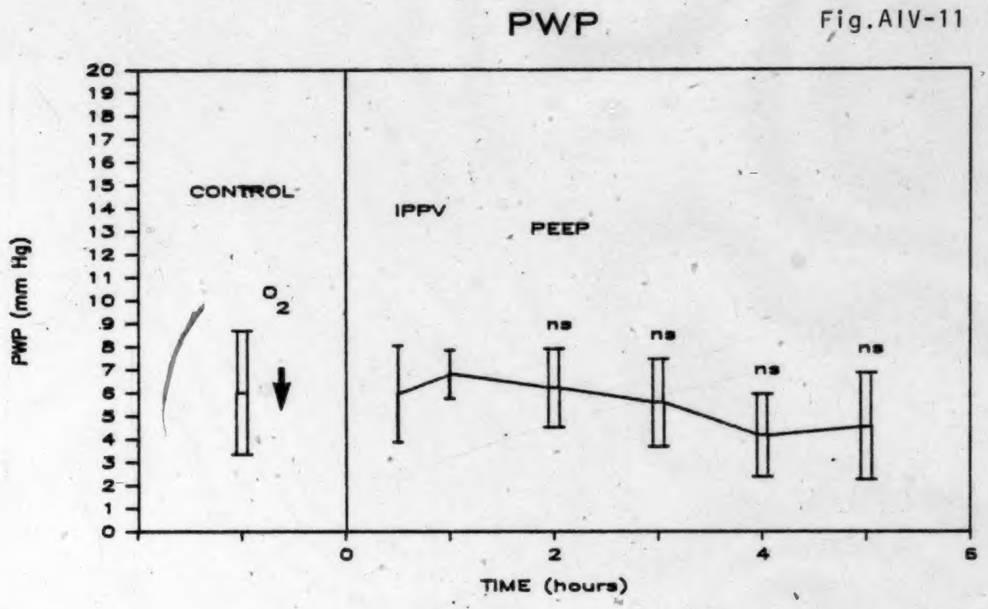


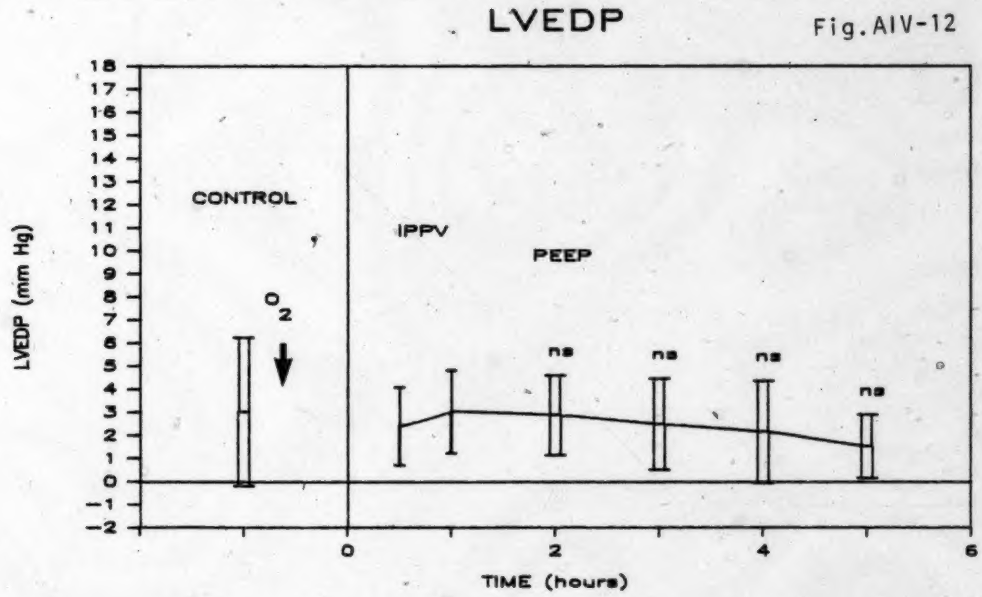
Figures AIV-7 and AIV-8: Average arterial PO_2 (top) and alveolo-arterial PO_2 gradients (bottom) changes before and after saline lavage of the lungs. Symbols as in Fig AIV-3.





Figures AIV-9 and AIV-10: Average arterial PCO_2 (top) and mean pulmonary artery pressure (bottom) changes before and after saline lavage of the lungs. Symbols as in Fig AIV-3.





Figures AIV-11 and AIV-12: Average pulmonary wedge pressure (top) and left-ventricular end-diastolic pressure (bottom) changes before and after saline lavage of the lungs. Symbols as in Fig AIV-3.

Fig.AIV-13

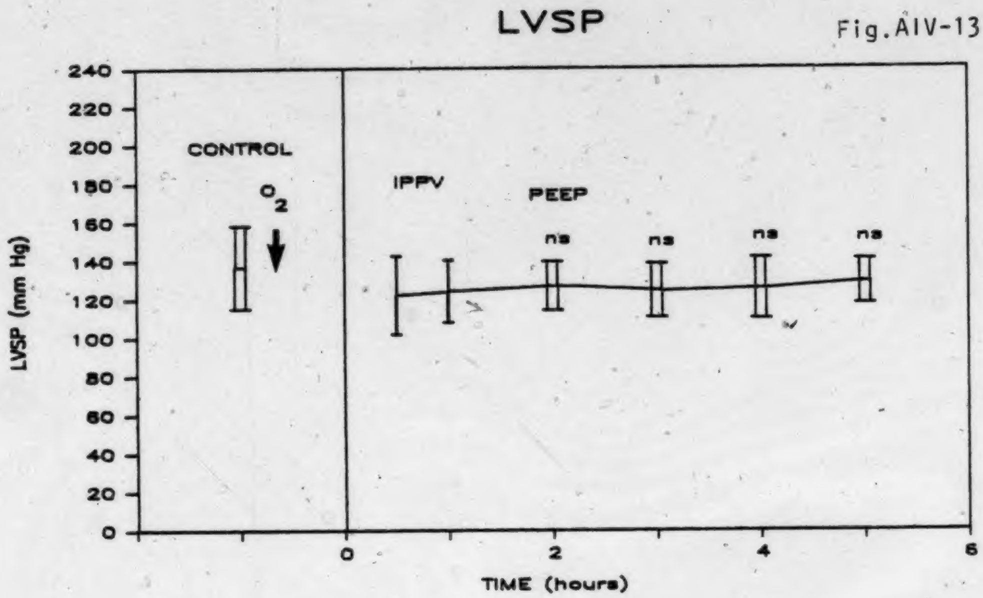
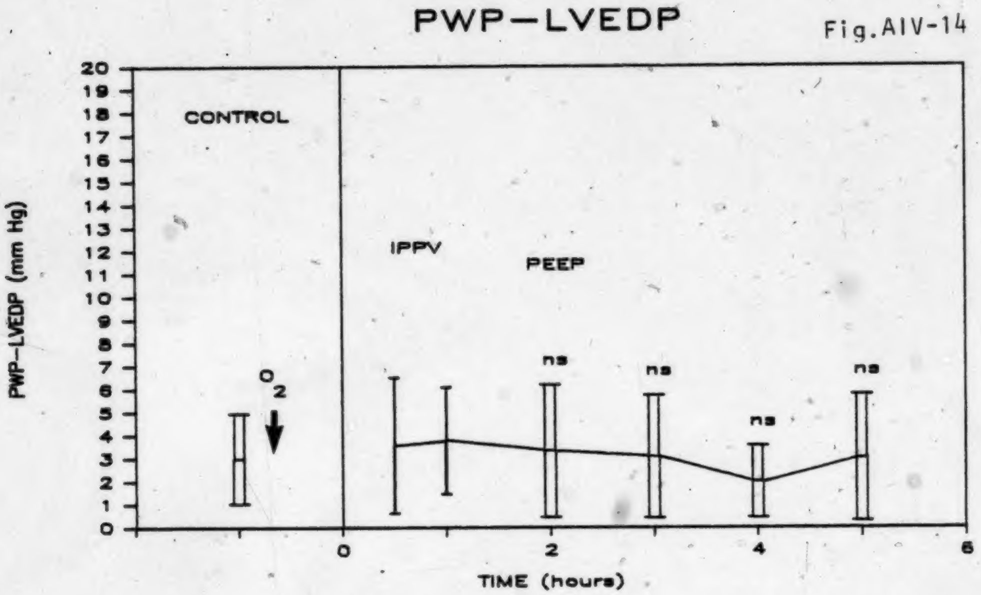


Fig.AIV-14



Figures AIV-13 and AIV-14: Average left-ventricular stroke work (top) and gradient pulmonary wedge pressure/left-ventricular end-diastolic pressure (bottom) changes before and after saline lavage of the lungs. Symbols as in Fig AIV-3.

APPENDIX V

IN VITRO STUDY OF THE EFFECT OF THERMISTOR VIBRATION ON FLOW MEASUREMENT BY THERMODILUTION

INTRODUCTION

When the first results of hemodynamic function during HFOV were obtained, it was surprising to find a significant decrease in $\dot{Q}$ (Chapter 1) in discordance with other author's findings (see Introduction). It was speculated that the mechanical vibration of HFOV could have some effect on the thermodilution measuring system and induce an error in the readings. To test this possibility, a simple bench study was designed, which consisted of measuring the fluctuations in resistance across the thermodilution catheter's electrical circuit, during vibration at high frequency. On a second test, the effect of catheter vibration on measurements of a flow of warm water was assessed.

METHODS

Effect of catheter vibration on electrical resistance: The thermistor circuit of a standard thermodilution catheter (Edwards Laboratories model 93A-301-7F) was included on a balanced Wheatstone bridge, with the output amplified and fed into a physiological recorder. The pen deflection was calibrated by immersing the thermistor in warm water at known temperature. A tracing of resistance across the thermistor circuit was obtained during vibration of different portions of the catheter at 20 Hz (Vortex mixer, model 12-812, Fisher Scientific Co.).

Effect of vibration on flow-measurement by thermodilution: To test the effect of vibration on flow measurement by thermodilution, the system depicted in Fig.AV-1 was used. It consisted of a large reservoir (15 Liters) filled with water at 37°C (measured with an electronic thermometer) which was circulated through a tubing by an adjustable-speed roller pump. The distal end of the tubing was occluded and had several side holes to enhance mixing; this terminal portion was introduced in a 300-ml plastic bag which acted as a mixing chamber. A side port in the tubing was used to introduce a thermodilution catheter (Edwards Laboratories model 93A-301-7F) so that the proximal port (P in Fig.AV-1) was upstream from the chamber, and the thermistor (T) was located at the chamber's outlet. The mixing chamber was connected with an eccentric cam to the motor shaft of the HFOV pump, to induce a 30-Hz vibration of the catheter and chamber. To measure flow through the system 3-ml boluses of ice-cold 5% dextrose solution were injected through the proximal port of the catheter and flow was calculated with a cardiac output computer (Instrumentation Laboratory model 9520; $\dot{Q}$ in Fig.AV-1). The speed of the roller pump was adjusted to produce different flows of water through the system, and 50 pairs of measurements (with and without chamber vibration) were performed when a steady state (of flow and temperature) had been reached. Correlation of values obtained with and without vibration was tested by a linear regression analysis.

RESULTS

Electrical resistance measurments: Vibration of the thermodilution catheter induced a significant fluctuation in resistance, in phase with the vibration (Fig.AV-2). In some cases the amplitude of the fluctuation was equivalent to a temperature change of near 0.5°C. Larger fluctuations were obtained when the catheter was vibrated and the thermistor was held motionless than when the opposite was done.

Flow measurements: Fig.AV-3 shows the flow measurements obtained during chamber vibration, plotted against values obtained without vibration;

the line of identity and the linear regression equation are also shown. There was a strong correlation between both sets of measurements ($p<2x10^{-7}$), which were situated very close to the identity line.

DISCUSSION

The vibration of the catheter induced a change in electrical resistance probably related to physical contact of the conducting wires inside the catheter, which presumably were not sufficiently insulated. Several catheters were tested and the same phenomenon was observed. The amplitude of the fluctuation was not influenced by keeping the electrical connection from moving, thus ruling out an artifact at this level. Also the results suggest that the thermistor itself was not the major factor responsible for the fluctuations in resistance.

The thermodilution catheters are calibrated to measure flows of blood, which has a different specific heat than water. Thus the measurements obtained in this study were not an accurate reflection of the flows of water. However this error can be expected to have the same magnitude during the vibration and non-vibration flow measurements, and would not affect the correlation between pairs of results.

After these experiments had been concluded, the most likely explanation for the lack of effect of vibration during flow measurements (despite the large artifact induced in the isolated catheter) was found: according to the manufacturer, the $\dot{Q}$ computer has a built-in 2.5 Hz low-pass filter (which filters-out the high-frequency changes in resistance).

Therefore, the finding of a decreased $\dot{Q}$ during HFOV was considered an accurate finding and not an artifact induced by HFOV.

Fig. AV-1

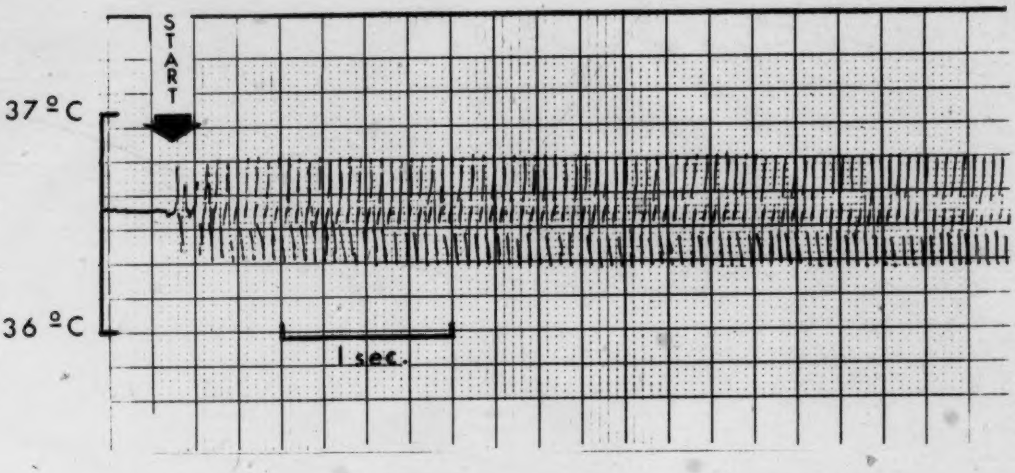


Fig. AV-2

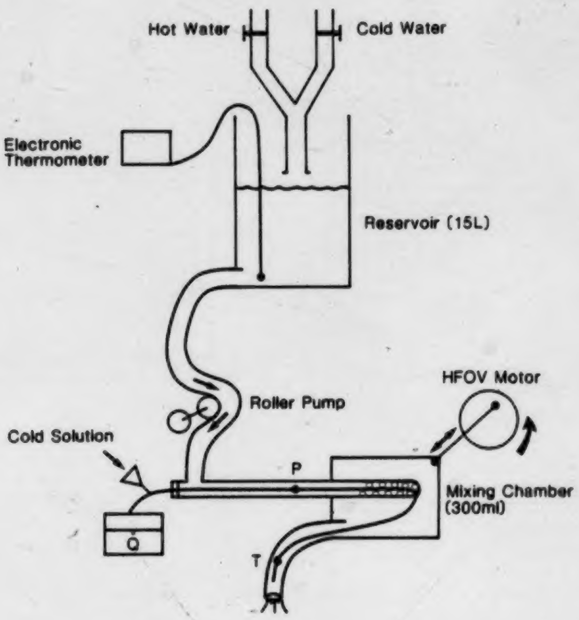

Hot Water
Cold Water
Electronic Thermometer
Reservoir (15L)
HFOV Motor
Roller Pump
Cold Solution
P
Mixing Chamber (300ml)
Q̇
T

Figure AV-1: Change in thermistor resistance (calibrated for temperature) during high-frequency vibration. Figure AV-2: Circuit used for the *in vitro* test of cardiac output measurement during vibration. $\dot{Q}$, cardiac output computer, T, catheter's thermistor.

Fig. AV-3

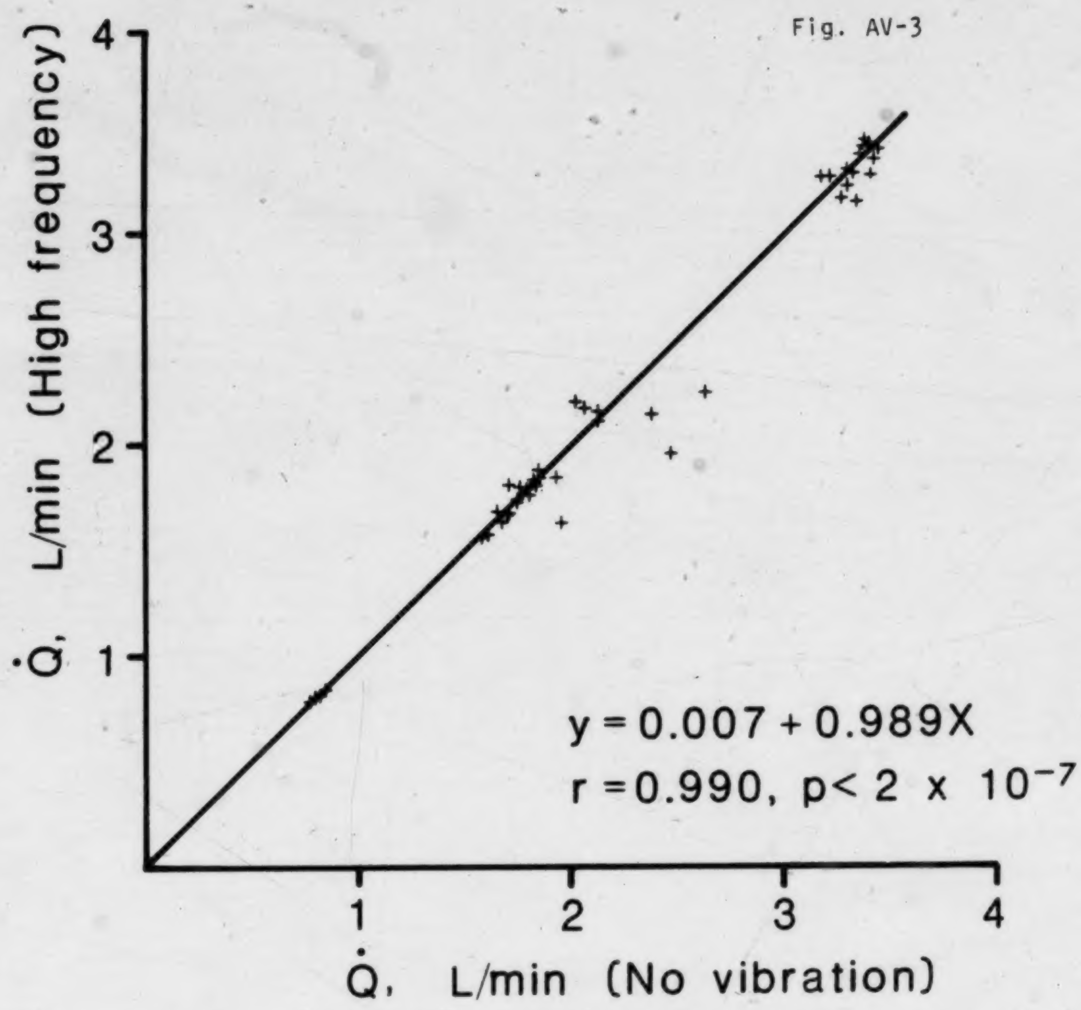


Figure AV-3: Flow measurements obtained with and without vibration of the thermodilution catheter. Insert, linear regression equation, correlation coefficient (r), and significance level.

APPENDIX VI

DESCRIPTION OF AN INEXPENSIVE FLOWMETER FOR LOW-FLOW MEASUREMENTS

INTRODUCTION

During the measurements of collateral ventilation (Chapter 6), it was necessary to accurately measure the flow of air going into the wedged segment, on a range too low to be assessed by flowmeters used clinically (bellow 1 L/min). Also, during the measurements of FRC by helium dilution (Chapter 2 Appendix IV) it was necessary to maintain a constant low flow of O_2 (equal to $\dot{V}O_2$ of the dogs) for several minutes. There are commercially-available rotameters for the ranges required (Kantes, Vineland, NJ) but they are expensive, and each flow range requires a different rotameter. In this chapter, a simple, accurate and inexpensive flowmeter for the desired range of measurements is described; it was constructed from materials readily available in the research laboratory.

DESCRIPTION OF THE FLOWMETER

The flowmeter consists of 3 main parts: resistive elements, measuring systems and safety features. It functions as follows: the gas is forced through the resistive elements creating a pressure gradient proportional to flow, which is assessed by the measuring systems. The safety features prevent spillage of water into the resistive elements and allow rapid release of excessive pressure in the system.

The resistive element consisted of three hypodermic needles (38.1 mm long) of different sizes (in this case, two 19-gauge and one 21-gauge needles were used) attached to three 3-way stopcocks (3W in Fig.AVI-1) which were connected to the flowmeter's inlet. The tips of the needles were inserted into the outlet tubing of the flowmeter; the points of contact were sealed with silicone glue (SG). By turning the stopcocks, the gas could be forced through one, two or all three needles.

Two measuring systems were incorporated into the flowmeter. The first consisted of two glass tubes (G in Fig.AVI-1) connected by a piece of Silastic tubing (SI). They were partially filled with distilled water which was colored with a red dye. A milimetric scale in one of the glass tubes (SC) permitted assessment of the water level. A 5-ml syringe (S4) was used to inject more water into the system to adjust the zero level. The second measuring system allowed for more accurate flow measurements (but is also very expensive). It consisted of a differential-pressure transducer (Statham PM5) which measured the difference in pressure between the inlet and outlet tubings (PM5). The amplified output of the transducer was displayed on a digital voltmeter (Hewlett Packard model 3430A) to allow fast and precise readings.

Two safety features were incorporated into the flowmeter. The first was a large-bore piece of tubing (B, Fig.AVI-1) which connected the flowmeter's inlet and outlet. During flow measurements this tubing was occluded by a quick-release clamp (CL). In case of excessive pressure buildup in the system (assessed by the water level) the clamp was released and the air escaped through the bypass tubing, avoiding the resistive elements. The second safety feature consisted of a reservoir, made out of the barrel of a 25-ml syringe (R); it was located at the tip of the glass tube in which the water level rose. In case of an accidental high pressure in the system, the overflow water was collected in the reservoir, and did not reach the transducer or resistive elements. The size of the reservoir was calculated to be able to contain all the water of the measuring system.

When an unknown flow of gas had to be measured, the bypass tubing was opened and all the needles connected in parallel The bypass was then slowly clamped, watching the level of the water in the measuring system. If the water went off scale before the bypass was completely occluded, the flow was too high to be measured unless larger-bore needles were used. If the pressure change was low, with the bypass occluded, the 3-way stopcocks were turned to force gas to flow through only two or one needles, and create a satisfactory pressure change. If the pressure change was still too low, the flow had to be measured with narrower needles.

The cost of the flowmeter (excluding the pressure transducer) was under 10 dollars.

CALIBRATION

The flowmeter was calibrated with known flows of air from a high-pressure source and measured (at the flowmeter's outlet) with a 9-L bell spirometer (Collins model 6001) and a stopwatch. A flow range of 11 to 796 ml/min was tested for different combinations of flowmeter needles. Actual flows ($\dot{V}$) were compared to the pressure drop (ΔP) measured by the PM5 transducer (in milivolts). Correlation between pressure and flow was tested by the least squares method and found to fit a logaritmic correlation equation (Fig.AVI-2). The different needle combinations corresponded to the following equations: 22 gauge, $\Delta P = 2.195 \times \dot{V}^{0.958}$ (r=0.993); 19 gauge, $\Delta P = 0.10035 \times \dot{V}^{1.224}$ (r=0.999); 19 G + 19 G + 22 G, $\Delta P = 0.0385 \times \dot{V}^{1.230}$ (r=-0.999). The range of flows tested was: 22 gauge, 11 to 81 ml/min; 19 gauge 36 to 360 ml/min; 19 G + 19 G + 22G, 192 to 796 ml/min.

DISCUSSION

This flowmeter was designed to measure a specific range of air flows, but the same principle could be used for a much larger range of flows by adding more and/or wider resistive elements (high flows) or using thinner and longer needles (lower flows). By turning the stopcocks, a new range of flows can be measured, without the need to disconnect any elements. The range of flows studied probably created some turbulence inside the resistive elements (and perhaps also the stopcocks), which explains the alinearity of the relationship $\Delta P/\dot{V}$. But it was found that the logaritmic transformation adequately corrected this alinearity giving a good correlation between ΔP and $\dot{V}$. The system was calibrated with air, and gases of different densities and viscosities would require other calibration equations. During the Helium-dilution experiments, oxygen was used but the flowmeter was utilized only qualitatively, to obtain a steady flow.

Fig. AVI-1

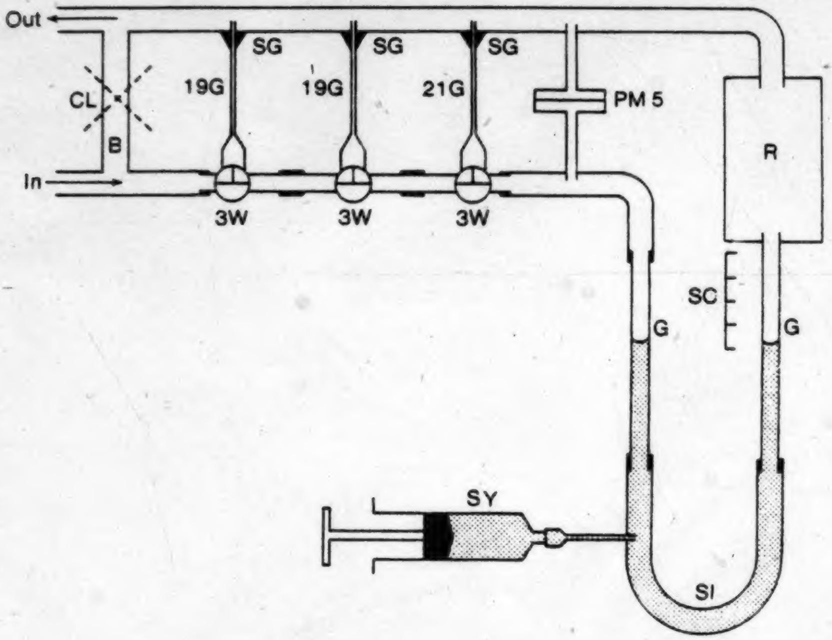

Out
In
CL
B
SG
SG
SG
19G
19G
21G
3W
3W
3W
PM 5
R
SC
G
G
SY
SI

Fig. AVI-2

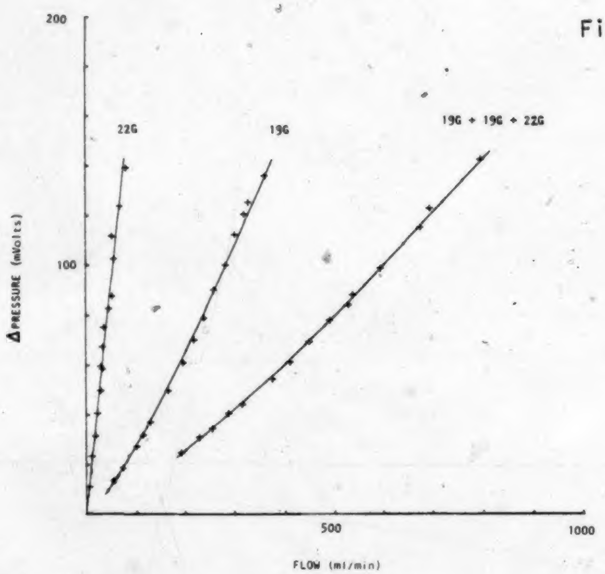


Figure AVI-1: Diagram of the flowmeter. B, by-pass tubing; CL, clamp; G, glass tubing; R, safety reservoir; SG, silastic glue; SI, silastic tubing; SY, syringe; 3W, three-way stopcocks;19G&21G, resistance needles. Figure AVI-2: Change in the flowmeter's pressure (measured in milivolts) with different needle combinations, and varying air flows.

EPILOGUE

GLOBAL DISCUSSION AND SUMMARY

This thesis has been arranged in independent chapters, each with its own discussion. The purpose of this epilogue is to provide an overview of the research involved comparing the findings with relevant data from the HFV literature.

The HFOV pump used for experimental work reported in this thesis is an airtight metal bellows that delivers its stroke volume into the ETT with only minor losses due to compression (Appendix I). However, even though entrainment induced by the respiratory circuit is minimal, a small fraction of the V_T (around 13.7% at 20 Hz) is lost through the proximal ETT opening. Most reports in the HFV literature do not include data on the dynamic performance of the ventilators used, which makes it very difficult to reproduce the findings or compare the results from different groups. The loss of a portion of the V_T with the present circuit could have been obviated by using a closed system like the one described by Ngeow and Mitzner (Ref. Introd. # 441) or a high-impedance circuit as described by Slutsky et al. (Ref. Introd. # 479). However, these systems are quite sophisticated, and usually include electronic servo-mechanisms to maintain $\overline{P}aw$. When this thesis was started such systems had not been developed. Later, when they appeared, it was decided not to modify the basic HFOV system used, in order to maintain a consistency throughout the research that would allow comparison between different experiments. For the same reason, when the more-versatile diaphragm ventilators were developed, they were not used in the place of the original bellows pump. The system used for the present studies has a performance similar to a more conventional diaphragm pump (Chapter 8) when used at the same $\overline{P}d$ and equivalent V_T (there are no reports in the literature comparing different types of HFOV pumps). However, it is surprising that the bellows ventilator could not perform adequately at low $\overline{P}d$, whereas a piston ventilator (which can be expected to perform very much like the diaphragm pump used for the experiments described in Chapter 8) can achieve satisfactory gas exchange at very low $\overline{P}aw$ (Ref. Introd. # 323). The reason for this is not clear, and perhaps is related to a more "efficient" bellows-pump circuit which loses only around 13.7% of the V_T, whereas a conventional piston-pump circuit can lose up to 66% (Ref. Introd. # 338). It could be speculated that the bellows pump induced a much larger drop in Pd during the "expiratory" part of the respiratory cycle, collapsing small airways and decreasing $\dot{V}/\dot{Q}$ ratios unless high $\overline{V}_L$ is maintained by increased $\overline{P}d$. This is supported by the fact that whenever the bellows pump was tried at low $\overline{P}aw$, there was a substantial drop in PaO_2; when the animals were switched back to IPPV, PaO_2 remained below pre-HFOV levels unless several sigh maneuvers were performed (Appendix I). This suggests that HFOV at low $\overline{P}aw$ induced atelectasis of some lung regions.

The present HFOV circuit induces a gas exchange similar to IPPV but with greater hemodynamic impairment (probably due to high $\overline{P}alv$ and $\overline{V}_L$; Chapter 1). As mentioned in the Introduction, there are several reports in the literature of hemodynamic impairment during HFV, probably related also to increased $\overline{V}_L$ and intra-pulmonary pressures. The findings of this thesis indicate that of these two factors, the effects of pressure are predominant: The observed increase in LVEDP as $\overline{P}d$ rose, without change in $\overline{SAP}$ (Chapter 4) suggests that a decrease in LV compliance was probably responsible for the decrease in $\dot{Q}$ (Chapters 1 and 3). Also, the hemodynamic changes observed during HFOV were equivalent to those during

PEEP when $\bar{P}d$ (and not $\bar{V}_L$) was matched (Chapter 3). Moreover, if the increase in $\bar{V}_L$ had been responsible for the hemodynamic impairment (through an increase in PVR), a decrease in LV preload (PWP and LVEDP) would be expected, but this was not observed. However, the large increase in PVR induced by HFOV (Chapters 1 and 3) suggest that distortion of the pulmonary vasculature induced by high lung volumes was present during these experiments. The data presented in Chapter 9C suggest that PG release did not mediate the effects of HFOV on the pulmonary circulation. There are no reports in the literature on the role of PG's on the hemodynamic response to HFV.

The changes in $\bar{P}d$ during HFOV induced a linear increase in $\bar{V}_L$ (at least in the range of 6 to 16 cm H_2O) and intrapulmonary vascular pressures, mainly CVP, $\overline{PAP}$, $\overline{PWP}$ and LVEDP (Chapter 4). The increase in lung volume observed during HFOV was complete within 1 min, and was stable for at least 16 min; higher frequencies induced a larger increase in $\bar{V}_L$ but there was a tendency for $\bar{V}_L$ to level off at 25-30 Hz (Chapter 2). There are no reports in the HFV literature of plethysmographic FRC measurements or the time course of the $\bar{V}_L$ changes.

In the initial experiments in which $\bar{P}aw$ and $\bar{V}_L$ were compared, it was observed that HFOV tended to induce a higher $\bar{V}_L$ than what was expected from $\bar{P}aw$ and the static P/V curves of the lungs (Chapter 15). Other reports in the literature also suggested at equivalent $\bar{P}aw$, $\bar{V}_L$ is higher during HFOV (Ref. Introd. # 402,460). This could be explained by a gradient in airway pressure generated during HFOV, which produced a $\bar{P}d$ substantially higher than proximal $\bar{P}aw$ (Chapter 9A). Several reports in the HFV literature have confirmed these findings (Ref. Introd. # 330,348,441,460,488). In spite of the increase in small-airway pressures, HFOV was found to increase Rcoll when compared to static distension of the lungs at the same volume (Chapter 6).

The effects of HFOV on mucociliary function were studied by measuring the rates of tracheal transport of radioactive markers. It was found that the influence of HFV and IPPV on TMTR was similar (Chapter 7); these findings agree with the data available in the literature (Ref. Introd. # 151,429).

To study the effects of HFOV on dogs with stiff lungs, pulmonary injury was induced by saline lavage (Appendix IV). The findings of these experiments (Chapter 5) agree with data available in the literature (Ref. Introd. # 335,371,402) in that HFOV induces higher $\dot{V}_L$ and PaO_2 than PEEP at similar $\overline{P}$aw. This saline-lavage model was used instead of the clasical oleic-acid model (Chapter 9F) because it induces a more-selective lung damage with less hemodynamic impairment.

For the statistical analysis of the results, a two-tailed paired t-test was usually employed because each animal was normally used as its own control and no obvious trends were expected. However, when a non-normal distribution of the data was suspected, non-parametric tests were used (Chapter 7). Also, when too many comparisons had to be made between groups, an analysis of variance (ANOVA) was used to avoid "overtesting" the data. One exception was Appendix III in which 3 similar methods had to be compared with a 4th one. In this case the use of several t-tests was justified to prevent the similarities between the first 3 methods from masking the differences with the 4th one. The differences between groups in the ANOVA analysis were tested with a Duncan's new multiple range test which is a more conservative approach than the least significant difference test. The correlation analysis, either linear or curvilinear, was performed by the least-squares method. The significance level was set at $p<0.05$ unless a statistical analysis was involved in the calculation of the data, in which case the significance level was decreased to $p<0.025$ (Chapter 1). This was done because the potential errors involved in the first statistical calculation could become added to the second test errors, and to avoid its influence the significance level had to be dropped. Data are presented as mean ± SD.

As the present HFOV pump required high $\overline{P}alv$ and $\overline{V}_L$ to achieve satisfactory gas exchange, and the deleterious effects on the cardiovascular function were probably related to these parameters, it is likely that other HFOV systems not requiring high $\overline{P}alv$ and $\overline{V}_L$ do not induce such hemodynamic derangement.

In summary, in this thesis a metal bellows high-frequency oscillator has been developed, characterized *in vitro*, and proven to be able to maintain adequate gas exchange in dogs with normal and stiff lungs. Also, the acute effects of HFOV using this sytem on dogs have been described in the following aspects of the cardiopulmonary function: pulmonary and systemic circulation, gas exchange, oxygen transport, lung mechanics and tracheal transport of particles.

As a continuation to this research on HFV, a model for whole-body EOV was developed in colaboration with Dr. H.E. Ward (H.E. WARD, J. AMENGOL, AND J.L. JONES. Ventilation by external high-frequency oscillation in cats. *J. Appl. Physiol.* 1984, in press), and for partial-body EOV in colaboration with Drs. F.G. Eyal and Z. Hayek (F.G. EYAL, Z. HAYEK, J. ARMENGOL, AND R.L. JONES. High-frequency negative pressure ventilation on the surfactant-deficient cat and rabbit model. Conference on high-frequency ventilation of infants. Salt Lake City, 1984)